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Carbohydrate Metabolism in "ACTIVE" AND "STATIC" HUMAN OBESITY

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THE ASSOCIATION of a decreased tolerance to carbohydrate with obesity in middle age is well documented.[1-7] On the other hand, absence of consistent findings with respect to a disordered carbohydrate metabolism in obesity[8-10] generally has tended to discourage further research on the subject. Unlike diabetes mellitus, where a constant and striking abnormality in carbohydrate metabolism is characteristic of the whole course of the disease, obesity is merely evidence that for a variable period of time a disturbance in energy balance occurred. Thus, although the continued presence of excess fat may have its own metabolic consequences,[8] the phase of obesity which can be studied with most profit would appear to be the period in which the excess fat actually is accumulating.

That this is the case is indicated by observations in experimental animals made obese by means of lesions placed in the anterior hypothalamus. Although conflicting findings with respect to associated abnormalities of carbohydrate metabolism in such animals have been reported,[11-13] it has been shown[14] that during the time their excess weight is accumulating, increased tolerance to carbohydrate also is observed. Animals with varying degrees of hyperphagia due to hypothalamic injury were studied from the standpoint of their carbohydrate metabolism. During the phase of their obesity in which they were still actively gaining weight, a high degree of correlation was found when proximate rates of weight gain were plotted against levels of nonfasted blood sugar. After obesity became established, carbohydrate tolerance proved to be normal or decreased. Thus, it is believed that observations on the carbohydrate metabolism of hypothalamic hyperphagic animals which fail to take into account their proximate rates of weight gain are necessarily difficult to interpret.

Despich and Hasenohrl,[15,16] Ogilvie,[17] Rony,[8] Godlowski,[18] and others have studied tolerance to carbohydrate in obese human subjects. None of them was able to find any consistent abnormality. However, several authors suggested that in obese subjects a tendency to secondary hypoglycemia after meals was associated with voracity and marked gain in weight. Moreover, a rough correlation appeared to exist between duration of the obesity and increase in glucose tolerance. These investigators did not subject their data to statistical analysis. How-

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TABLE I
Classification of Obese Subjects

Subjects	Age	Height (In.)	Weight (Lb.)	Desirable Weight	% Above Desirable Weight	Duration, in Years	Weight Trend	Phase of Obesity
1	30	65	180	127–135	37.40	25	+	Active
2	34	66	221	130–140	63.70	9	+	Active
3	47	62	210.5	117–125	73.55	25	+	Active
4	37	63	170.5	120–128	38.31	21	—	Active
5	44	63.25	163	121–129	30.40	7	0	Active
6	36	60	135	112–120	25.86	1	—	Active
7	49	62.5	186.5	118–127	51.63	28	—	Static
8	32	62.75	145	119–128	17.89	27	—	Static
9	32	62	146	117–125	20.66	27	—	Static
10	28	65.75	251	130–140	85.92	23	—	Static
11	46	64.25	173	125–133	34.11	34	—	Static
12	36	64.75	239	126–134	83.85	24	0	Static

ever, when such data are so analyzed,[19] the correlation between activity and duration of the obesity on the one hand and increased tolerance to glucose on the other is found to be significant. In these studies, glucose tolerance curves in early obesity proved to be lower or displayed a more frequent tendency to drop to hypoglycemic levels than did the tolerance curves of normal subjects or subjects with arrested obesity of long standing.

Accordingly, the carbohydrate tolerance of obese women and control subjects of the same sex, height, and age was studied in an attempt to determine whether a correlation could be found between phase of obesity and pattern of glucose tolerance. Since deviations from normal in the carbohydrate tolerance of obese individuals, if they exist, are likely to be small, abrupt changes in diet and rigorous experimental procedures may obscure them. Thus, it seemed important that blood sugar changes in obese individuals and their controls, whether in response to food or to ingested glucose, be studied with all the subjects maintained in their natural dietary setting.

Procedure and Results

Subjects

The relevant data concerning the obese subjects and their controls are in Tables I and II. The obese subjects were more than 20 per cent above the mid-point of the desirable weight range for their height (medium frame).[21] The obese subjects were regarded as being in the "active" phase (a) if they had been gaining appreciable amounts of weight at the time the study was performed, regardless of the duration of obesity, or (b) if their obesity was of relatively recent onset (during adulthood), regardless of whether strict dieting had interrupted the progress of weight gain. "Static" obesity was defined as obesity of long duration (usually since childhood) and arrested for a long time, either spontaneously or by diet. In this series, the members of the group in the active phase of obesity, with one exception, a woman (No. 1), who was gaining weight very rapidly (30 lb. in the 4 preceding months) at the time of the study, had become obese in adulthood. Members of the group in the static phase of obesity (with one

TABLE II
Data on Normal Weight Controls

Subjects	Age	Height, (In.)	Weight, (Lb.)	Desirable Weight	% of Desirable Weight
13	28	65.5	119.25	129–137	−11.47
14	33	66.75	140	133–143	+1.45
15	52	61	112.75	114–122	−4.45
16	41	65.25	136	128–136	+3
17	48	65	125	127–135	−4.48
18	38	64	127	124–132	−0.08
19	32	61.5	106	115–123	−17.83
20	32	62.25	116	118–126	−4.92
21	28	62	114.5	117–125	−5.37
22	29	64	114	124–132	−10.94
23	45	65.75	123	129–138	−8.21
24	31	64	126	124–132	−1.56

exception—No. 7—who had become obese 21 years previously and was losing weight at the time of the study) had been obese since childhood.

For each obese woman, a control subject of the same height and age was selected. The weights of the control subjects were within the accepted range of desirable weights[21] and had spontaneously remained within that range for many years.

Methods

Venous blood was always obtained from the antecubital area. Capillary blood was collected by direct pipetting from a finger tip, after cutaneous puncture. When capillary and venous samples were obtained concurrently, sampling times were virtually simultaneous. The subjects were studied in the resting state in a comfortable warm room kept at constant temperature.

The Somogyi-Nelson semi-micromethod[22,23] was used to measure glucose in whole blood. Determinations were done in duplicate on 0.2-ml. samples. The method of Fiske and Subbarow[24] was used to determine serum inorganic phosphorus.

In all cases, diet records were kept for the day preceding each test and for another day in the interval between the two tests. Dietary calculations were carried out by the method of Leichsenring and Donelson-Wilson.[25]

Plan

Twelve obese women and twelve matched control non-obese subjects were studied (Tables I and II). Two types of carbohydrate tolerance study were carried out on each subject. On one occasion, values for venous glucose were determined before and at 15-minute intervals for an hour following ingestion of a self-selected meal at noon. At another time, the same subjects were given 50 Gm. of glucose in place of lunch and a similar schedule for blood sampling was used. Caloric, protein, carbohydrate and fat content of the self-selected meals and of all food eaten the day preceding the carbohydrate tolerance studies were calculated in each case; these are summarized with appended statistical analysis in Tables VII and VIII.

Results

Data concerning the blood glucose changes after the self-selected meals and after the orally administered glucose were converted into percentage increases over the pre-meal values. The information concerning these glucose changes and also the details of the composition of the self-selected meals are given in Tables III and IV. Statistical comparisons between the two groups are presented in Tables V and VI.

It was found (Table VII) that no statistically significant differences existed between the caloric, protein, fat, and carbohydrate content of the self-selected meals consumed in the meal tolerance test by the six women in the group in the active phase of obesity and that consumed by their normal weight controls. The women in the static group had a significantly smaller carbohydrate intake than their controls.

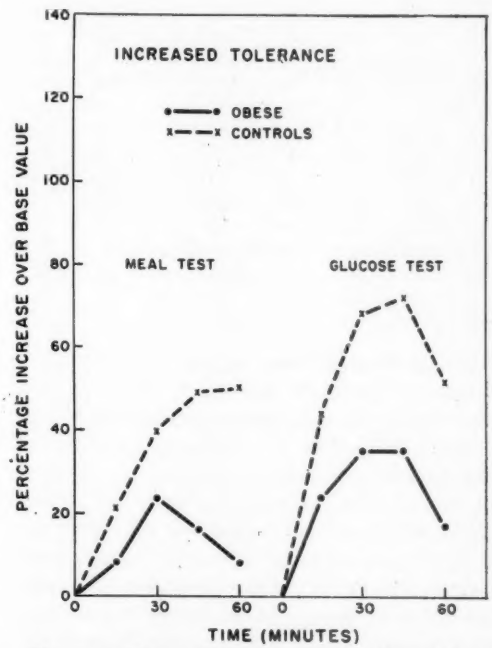

Figure 1. Glucose tolerance curves of obese patients (active obesity) and normal weight control subjects following (a) self-selected meal and (b) oral glucose.

TABLE III

Percentage Increase Over Base Value of Venous Blood Sugar in 12 Obese Subjects

Subjects No.	After the Ingestion of a Self-Selected Meal: Composition of Meal: Calories	Pro. (Gm.)	Fat (Gm.)	CH_2O (Gm.)	Percentage Increase at (Min.): 15	30	45	60	After Oral Administration of 50 Gm. of Dextrose: Percentage Increase at (Min.): 15	30	45	60
1	600	24.4	26.1	66.2	9	19.4	4.5	9	24.2	58.1	54.8	22.6
2	384	19.4	20.4	30	20.8	22.1	24.7	24.7	12.3	44.9	47.1	44.9
3	458	17.4	8.2	50.8	1.1	15.2	15.2	17.4	26.8	38.7	35.4	11.8
4	335	14	10.6	45	0	3.4	−4.6	−13.8	18.2	14.3	5.2	−5.2
5	526	22.4	22.5	59.7	10.3	39.7	42.3	25.6	33.8	36.3	38.8	7.5
6	320	12.5	16	31	9.4	25.6	12.1	−17.5	27.4	17.9	28.6	19
7	388	21	18	35.5	13.7	41.1	64.4	64.4	75	86.7	141.7	158.3
8	400	19.4	21.8	30	39.3	39.3	103.6	132.1	21.4	77.4	116.7	160
9	535	25.6	37.9	21.9	16.9	76.3	69.5	76.3	72.7	140	174	184
10	272	12.2	11.2	30	2.2	15.7	16.9	29.2	31.1	100	151.4	178.4
11	924	39.5	54.8	68.5	6.6	55.3	22.4	−5.3	32.4	50.7	52.1	60.6
12	359	13.4	11.3	52.7	4.2	23.6	34.7	27.8	12.9	53.5	74.3	91.4

TABLE IV

Percentage Increase Over Base Value of Venous Blood Sugar in 12 Normal Weight Controls

Subjects No.	After the Ingestion of a Self-Selected Meal: Composition of Meal: Calories	Pro. (Gm.)	Fat (Gm.)	CH_2O (Gm.)	Percentage Increase at (Min.): 15	30	45	60	After Oral Administration of 50 Gm. of Dextrose: Percentage Increase at (Min.): 15	30	45	60
13	493	19.8	28.5	42	38.7	38.7	45.2	45.2	54.8	137.1	135.5	88.7
14	967	33.5	47.7	102.7	45.2	42	58.1	38.7	29.4	29.4	20	−8.4
15	information not provided				6.1	37.9	68.2	72.7	74	139.7	165.8	156.2
16	323	13.1	8.2	50.8	20.9	20.9	10.4	Not done	38.6	22.8	24.6	15.8
17	344	12.7	16.5	35.3	5.7	60	81.4	57.1	36	32	34.7	9.3
18	645	28.8	29.9	65.7	11.1	31.9	33.3	11.1	28.9	49.4	54.2	49.4
19	456	10.5	13.4	75.6	16.4	100	117.9	59.7	56.7	55	80	126.7
20	1022	36.1	43.3	122.4	−1.3	43.6	41.0	21.8	8.5	0	25.6	26.8
21	583	32.5	15.9	76	34.8	83.3	84.8	74.2	76.4	141.8	194.5	225.5
22	980	32.9	39.9	118.4	0	17.8	28.8	28.8	8.4	10.8	41	49.4
23	591	23	22.2	80.2	8.3	44	53.6	54.8	31.3	66.3	109.6	124.1
24	643	32.3	31.4	57.8	39.4	43.2.	46.5	35.2	32.9	37	67.1	69.9

Of the twelve obese women, six displayed markedly increased tolerance, both to glucose and to meal carbohydrate, compared to their controls (Fig. 1). These obese subjects had blood sugars which were falling between 30 and 45 minutes after the test meal, while the values for blood glucose of the other six obese subjects still were rising at the one-hour mark. This group with increased tolerance was also the group which, according to criteria already cited, fell into the category of active obesity. On the other hand, the obese women with normal or decreased tolerance were uniformly in the static phase of obesity.

One of the subjects with typically increased tolerance to carbohydrates was given a standard intravenous glucose tolerance test (Fig. 2). In terms of results previously obtained in similar studies,[26] she also displayed an increased tolerance to 25 Gm. of intravenously given glucose.

Discussion

In this series of obese subjects, the association of "increased tolerance" to glucose and active obesity was invariable. Increased toler-

ance here is taken to mean a statistically significant difference between the normal and actively obese groups in percentage increase over the pre-meal or pre-test levels of blood glucose in the first hour. In the case of the oral glucose tolerance test, a high degree of significance was found to exist for the values at 15 and 30 minutes; in the case of the meal, at 30, 45, and 60 minutes. The results of this preliminary study are particularly interesting because they are consistent with the findings obtained in experimentally obese animals, which were discussed earlier. It will be recalled that in such surgically treated animals an excellent correlation was observed between non-fasted (venous) blood glucose and proximate rate of weight gain.

The existence of a metabolic abnormality in the actively obese subjects is further indicated by the finding that similarly increased tolerance was observed when glucose was administered intravenously rather than orally. Also, although the important influence of prior diet on glucose tolerance is well known, it can be seen in Table VII that the obese subjects consumed significantly less carbohydrate and fewer calories during the 24 hours preceding the meal test than did the normal weight controls. If anything, one would expect a decreased tolerance as a result of such a diet. Accordingly, the significance of the increased tolerance shown by the actively obese subjects is enhanced.

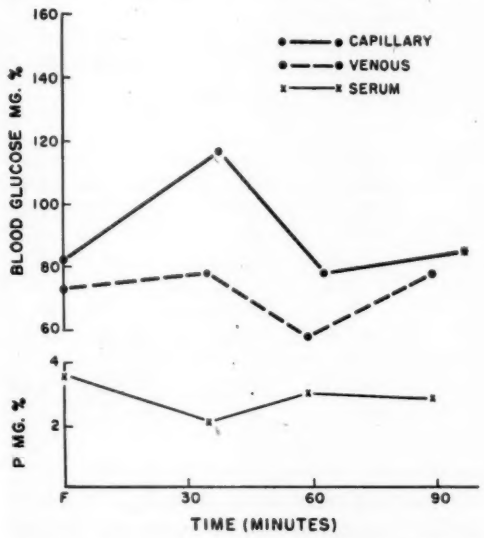

Figure 2. Arterial and venous glucose tolerance curves following intravenous administration of 25 Gm. of glucose to an obese patient who displayed increased tolerance to orally administered glucose as well (Patient 4). Associated changes in serum inorganic phosphorus also are shown.

If the existence of a metabolic disorder in the actively obese group can be postulated, a number of alternative explanations are available. The increased rate of disappearance of glucose from blood in these subjects may be accounted for by either of two mechanisms which are not mutually exclusive. One involves increased lipogenesis, the other decreased oxidation of fat and proportionately increased oxidation of glucose. Recent studies[27] done on hereditarily obese mice of the Obob strain[28,29,30] showed a markedly decreased oxidation of administered radioacetate, the unoxidized acetate fragments being converted to fatty acids. These mice exemplify a form of obesity in which decreased utilization of fat seems to be in the primary lesion. Increased tolerance to glucose in human subjects may be due to decreased lipolysis and a relative increase in carbohydrate oxidation as long as carbohydrate is readily available. The other possibility involves either a "relative" or an "absolute" hyperinsulinism and increased lipogenesis, as discussed in detail elsewhere.[14]

This evidence of disordered carbohydrate metabolism in actively obese animals and human subjects is susceptible of interpretation in the light of the glucostatic theory of food intake regulation.[31,32] If variations in blood glucose exert a regulatory influence on food intake as is postulated in the glucostatic theory, the increased intake of obese individuals becomes intelligible in physiologic terms. Hunger is one of the homeostatic mechanisms which acts to insure an adequate supply of carbohydrate to the organism. Need for further intake of food is appropriately signaled by the onset of "metabolic hypoglycemia." Metabolic hypoglycemia in turn is indicated by rapid shrinkage of arteriovenous glucose differences in the periphery.[33] Under normal conditions, when arteriovenous glucose dif-

TABLE V

Statistical Analysis of Percentage Increase over Base Value of Venous Blood Glucose Following Ingestion of a Self-Selected Meal and an Oral Dextrose Test in Obese Subjects in "Active" Obesity and Their Controls

	Mean Percentage Increase over Base Value					
	6 Obese Subjects	6 Desirable Weight Subjects	Difference between Means	t	Degrees of Freedom	Probability of t
			Meal Test			
Time after End of Meal	*No. 1–6*	*No. 13–18*				
15 min.	8.43	21.28	−12.85	1.68	10	$0.2 > P > 0.1$
30 min.	22.56	38.56	−16	2.22	10	$0.05 > P > 0.02$*
45 min.	15.70	49.43	−33.73	2.72	10	$0.05 > P > 0.02$*
60 min.	7.56	50.12	−42.56	3.27	9	$0.01 > P > 0.0001$†
			Dextrose Test			
Time after Ingestion of Solution						
15 min.	23.78	42.61	−19.83	2.53	10	$0.05 > P > 0.01$*
30 min.	35.03	68.40	−33.37	4.53	10	$0.01 > P > 0.001$†
45 min.	34.98	72.46	−37.48	1.41	10	$0.2 > P > 0.1$
60 min.	16.76	51.83	−35.07	1.25	10	$0.3 > P > 0.2$

* Significant at the 0.05 level.

† Significant at the 0.01 level.

TABLE VI

Statistical Analysis of Percentage Increase over Base Value of Venous Blood Glucose Following Ingestion of a Self-Selected Meal and an Oral Dextrose Test in "Static" Obesity and Their Controls

	Mean Percentage Increase over Base Value					
	6 Obese Subjects	6 Desirable Weight Subjects	Difference between Means	t	Degrees of Freedom	Probability of t
			Meal Test			
Time after End of Meal	*No. 7–12*	*No. 19–24*				
15 min.	11.61	16.26	−4.65	0.39	10	$0.7 > P > 0.6$
30 min.	41.88	55.40	−13.52	0.88	10	$0.4 > P > 0.3$
45 min.	51.91	62.10	−10.19	0.50	10	$0.6 > P > 0.5$
60 min.	54.08	45.75	+8.33	0.39	10	$0.8 > P > 0.7$
			Dextrose Test			
Time after Ingestion of Solution						
15 min.	40.91	35.70	+5.21	0.27	10	$0.8 > P > 0.7$
30 min.	84.71	51.81	+32.90	1.32	10	$0.3 > P > 0.2$
45 min.	118.45	86.30	+32.15	2.63	10	$0.05 > P > 0.02$*
60 min.	138.91	104.73	+34.18	0.36	10	$0.8 > P > 0.7$

* Significant at the 0.05 level.

ferences in men remain negligible, hunger is invariably present. The increase in glucose tolerance observed in actively obese subjects suggests that such persons return to a state of metabolic hypoglycemia earlier than do normal weight individuals; hence satiety is more transient.

This discussion of a physiologic basis of obesity does not intend to imply that psychologic factors are not important. However, it can hardly be said that the psychologic aspects of obesity have been neglected in the past. Obesity can be a symptom of a great many disorders. In this discussion, an at-

TABLE VII

Statistical Comparison of the Mean Caloric and Nutrient Intake of Obese Subjects with That of Their Controls Prior to or on the Occasion of the Self-Selected Meal Test

	Nutrient	Subjects: Obese *No. 1–6*	Subjects: Controls *No. 13–18*	Difference between Compared Means	t	Degrees of Freedom	Probability
Noon Meal Test	Calories	437	554	−117	0.99	9	0.4 > P > 0.3
	Protein (Gm.)	18.35	21.58	−3.23	0.74	9	0.5 > P > 0.4
	Fat (Gm.)	19.68	26.16	−6.48	0.98	9	0.4 > P > 0.3
	CH_2O (Gm.)	46.93	59.30	−12.37	0.40	9	0.7 > P > 0.6
Day before Meal Test	Calories	1380	2291	−911	2.39	10	0.05 > P > 0.02*
	Protein (Gm.)	57.05	82.50	−25.45	1.66	10	0.2 > P > 0.1
	Fat (Gm.)	53.51	93.38	−39.87	2.17	10	0.1 > P > 0.05
	CH_2O (Gm.)	166.50	260.93	−94.43	2.55	10	0.05 > P > 0.02*
		No. 7–12	*No. 19–24*				
Noon Meal Test	Calories	498	713	−134	1.74	10	0.2 > P > 0.1
	Protein(Gm.)	21.9	27.9	−5.6	1.07	10	0.4 > P > 0.3
	Fat (Gm.)	25.8	27.7	−2.1	0.23	10	0.9 > P > 0.8
	CH_2O (Gm.)	39.8	88.4	−48.6	3.83	10	0.01 > P > 0.001†
Day before Meal Test	Calories	1691	2757	−1066	4.10	10	0.01 > P > 0.001†
	Protein (Gm.)	71.6	90	−18.4	1.55	10	0.2 > P > 0.1
	Fat (Gm.)	75.9	120.8	−44.9	2.84	10	0.02 > P > 0.01*
	CH_2O (Gm.)	198	331	−133	3.91	10	0.01 > P > 0.001†

* Significant at 0.05 level.
† Significant at 0.01 level.

TABLE VIII

Statistical Comparison of the Mean Caloric and Nutrient Intake of Obese Subjects and Their Controls for the Day Preceding the Dextrose Test

	Nutrient	Subjects		Difference between Compared Means	t	Degrees of Freedom	Probability
		No. 1–6	*No. 13–18*				
Day before Dextrose Test	Calories	1661	1781	−120	0.46	10	0.7 > P > 0.6
	Protein (Gm.)	53.06	71.11	−18.05	1.55	10	0.2 > P > 0.1
	Fat (Gm.)	71.41	84.31	−12.90	0.64	10	0.6 > P > 0.5
	CH_2O (Gm.)	198.26	184.65	+13.61	0.30	10	0.8 > P > 0.7
		No. 7–12	*No. 19–24*				
Day before Dextrose Test	Calories	1531	2242	−711	6.12	10	0.001 > P > †
	Protein (Gm.)	62	70.1	−8.1	1.98	10	0.1 > P > 0.05
	Fat (Gm.)	76.4	108.2	−31.8	1.43	10	0.2 > P > 0.1
	CH_2O (Gm.)	148	248.7	−101.7	2.63	10	0.05 > P > 0.02*

* Significant at the 0.05 level.
† Significant at the 0.01 level.

tempt has been made to delineate a physiologic mechanism which may underly one form of disturbance of energy equilibrium.

In summary, the results obtained in this pilot study of carbohydrate tolerance in obesity again indicate the importance of taking into account not only the age, previous diet, and state of nutrition of the obese subject in question, but also the duration of the obesity and, most important, its proximate activity—the rate of weight gain during the weeks and months preceding the test. Such subjects should be studied in their natural dietary setting as well as under laboratory-type conditions.

It is believed that undue emphasis has been

placed on the fact that widely diverse findings are obtained when carbohydrate tolerance is studied in obese subjects. Such findings may all be individually valid, but they require interpretation in the light of the many variables which influence carbohydrate tolerance and, particularly, the activity of the obesity at the time the carbohydrate tolerance is being studied. The so-called "hyperglycemic" phase of late obesity has properly been stressed, and the connection between obesity and diabetes undoubtedly requires repeated emphasis. Yet consideration of equally important changes in carbohydrate metabolism that may be found in early active obesity should not be neglected.

In view of the "glucostatic" theory of food intake regulation, it may be suspected that even if such an increased tolerance to carbohydrate does not actually initiate obesity, it may help to perpetuate it. Thus, further elucidation of this relationship may prove to be of practical as well as theoretical interest.

Finally, it must be emphasized that the authors believe that the type of active obesity described here does not represent the only type of active obesity which may be due to impaired carbohydrate metabolism. It has already been mentioned that both hypoglycemia and "metabolic hypoglycemia" correspond to decreased arteriovenous differences and increased hunger of food intake.[32] This has been demonstrated to be true in diabetic rats,[34] in hereditarily obese-hyperglycemic mice,[29] as well as in uncontrolled diabetic, in hunger diabetic and in cortisone-treated human subjects.[35] To the type of hyperphagia described here and corresponding to the early shrinkage of an initially abnormally large arteriovenous glucose difference must be added that due to impaired phosphorylation of glucose,[29,34] causing permanently decreased arteriovenous differences and consequently high glucose tolerance. In man, as in the experimental animal,[34] abnormally increased or decreased glucose utilization and tolerance may have the same etiological significance with respect to hyperphagia.

Summary

Two groups of obese women, believed to be representative respectively of "active" and "static" obesity, were studied from the standpoint of tolerance to carbohydrate by means of dextrose and meal tolerance tests. Desirable weight subjects matched with respect to height and age served as controls. It was found that, compared to their controls, the obese subjects in the active phase of obesity displayed a markedly increased tolerance to carbohydrate after ingestion of self-selected meals and also after test doses of dextrose.

The importance of distinguishing between the active and static phases of obesity in the interpretation of metabolic data obtained from obese patients is stressed. The significance of increased tolerance to carbohydrate as it relates to regulation of food intake is discussed.

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Resumen

Metabolismo de los hidratos de carbono en la obesidad humana "activa" y "estatica"

Dos grupos de obesas que, segun se creía, representaban, respectivamente, la obesidad "activa" y "estática" han sido estudiados desde el punto de vista de la tolerancia a los hidratos de carbono, mediante pruebas de tolerancia a la dextrosa y a las comidas. Mujeres de peso normal con respecto a su edad y altura servían de control. Se halló que las obesas del grupo en la fase activa de la obesidad mostraron una tolerancia marcadamente aumentada a los hidratos de carbono después de la ingestión de comidas autoseleccionadas, y también después de dosis test de dextrosa.

Los autores insisten en la importancia que tiene el distinguir entre las fases activa y estática de la obesidad en la interpretación de los datos metabólicos obtenidos de pacientes obesos. Se discute el significado de la aumentada tolerancia a los hidratos de carbono en su relación a la regulación de alimentos ingeridos.

Fat Meat for Fat Men?

As if all the conflicting evidence on how to reduce weren't confusing enough, we have it on the highest—if not the latest—authority that fat men should eat fat meat—"because the smallest amount of it is filling." Futhermore, "they should eat only one meal a day, take no baths, sleep on hard beds, and walk around with as little clothing as possible."

The authority? Hippocrates, in his "Regimen for Health."

An Alternate Approach to THE PROBLEM OF OBESITY

By A. W. PENNINGTON, M.D.

IN THE PATHOGENESIS of obesity, two facts may be taken as axiomatic: first, a disproportion exists between caloric intake and output; and second, the size of the adipose tissues increases. These two simple facts are sometimes taken as a complete explanation of obesity, for it is tempting to draw from them the conclusion that the person who becomes obese merely eats too much and therefore adds flesh to his body. This view of obesity, in all its simplicity, appears to derive justification from the practical consideration that, in order to lose weight, the caloric intake must be less than the expenditure. In its support, the law of conservation of energy is frequently mentioned, the implication being that any other explanation of obesity violates this law.

The explanation of obesity as the result of simple overfeeding, however, rests on two assumptions which, though not immediately apparent, are inevitably bound up with it. These are (1) that the regulation of appetite has its basis in individual habit or custom, and (2) that the regulation of fat storage is a passive process, the size of the adipose deposits responding to no other influence than the balance between caloric intake and output. These are necessary assumptions in the concept of obesity as a result of careless or perverted eating habits, as hypothecated by Newburgh,[1] for they leave no physiological force or circumstance to oppose the conscious exercise of will power in the control of the food intake. Many clinical and experimental observations on appetite and fat storage, however, seem to challenge the basic assumptions of this theory of obesity and to suggest other, equally attractive, hypotheses.

From the E. I. du Pont de Nemours & Co., Wilmington, Delaware.

THE REGULATION OF APPETITE

A physiological regulation of the appetite was first suggested by general principles of homeostasis. Many observers have commented on the precision with which the human organism maintains constant weight over long periods of time, though food is taken in as it is provided or desired and is utilized as conditions may demand;[2,3a,4] and nutrition experiments have given confirmatory evidence.[5,6a] The resistance of the organism to change from an established level of body weight appears to be further evidence of a homeostatic regulation of appetite. This is apparent in the difficulties encountered by lean individuals in their attempts to gain weight, as well as by obese individuals in their attempts to reduce. It would appear that the appetite, far from being a completely independent function, is but part of a complex mechanism for assuring an appropriate intake of food, very much as a conscious desire to breathe participates in the homeostatic regulation of the blood and tissue gases.

When obesity develops there is an increased caloric intake in relation to caloric output during the period of weight gain. Rony has called this the "dynamic phase" of obesity, in contradistinction to the "static phase" in which the weight, though excessive, remains constant.[3b] Sometimes several such periods are seen. During the static phase, which may persist for a long interval of time, the caloric intake is balanced against the caloric output. The existence of this phase is a common observation in human obesity; and it is regularly observed in the hereditary obesity of mice[7] and in the experimental hypothalamic obesity of animals[8]. An upward readjustment of the mechanisms controlling appetite appears to

occur, with the balance of caloric intake to output becoming reëstablished at a higher level of body weight, very much as the balance between heat production and dissipation is established at a higher level of body temperature in continuous fever.

The disproportion between caloric intake and output during the phase of obesity in which weight is being gained seems, therefore, more difficult to explain than has sometimes been supposed. As Waife[9] expressed it, "It is not enough to say that people are fat because they eat too much; it is necessary to find out *why* they eat so much." An understanding of the pathogenesis of obesity, it seems, must be sought in the nature of the readjustment which takes place in the appetite-regulating mechanism, causing the weight to change from one level to another and then to resist change from that level.

There is abundant proof of an appetite-regulating center in the hypothalamus, and of its role in the pathogenesis of obesity. Destructive lesions here regularly produce obesity in experimental animals;[8] and it appears that structural damage to this area accounts for the obesity which follows some mild cases of encephalitis.[10] In the absence of gross organic changes in the hypothalamus, it is probable that obesity may result from alterations in the sensitivity of this highly specialized tissue. Jolliffe[11] has postulated that the sensitivity of the appetite-regulating center may be altered by habitual overfeeding, a concept which differs in no essential way from that of Newburgh, for it assumes an habitual or customary intake as the predominating influence on the regulation of appetite. Waife,[9] in 1947, suggested an alteration in the sensitivity of the appetite-regulating center as the result of psychic stress and the well-recognized influence of this on the autonomic nervous system. This concept would explain the definite, quantitative change in weight from one level to another so often observed in the obese. It takes cognizance of the precision with which the appetite is balanced to energy needs under normal conditions and offers a rational explanation for its derangement in the obese. The specific treatment of obesity due to this cause would of course be psychotherapy.

The maintenance of constant weight over long periods of time in spite of variations in energy expenditure from day to day indicates that the appetite-regulating center cannot be conceived of as being "set" rigidly to negotiate the ingestion of a fixed amount of food. Rather, it appears to be a coordinating center with great flexibility, on which somatic influences act afferently to insure an intake of food which varies appropriately under varying circumstances. This would mean that the ultimate regulator of the appetite is the energy requirement of the organism, a concept which is firmly held by many investigators and which appears to be confirmed by a number of nutrition experiments.[5,6b,12] It seems possible, therefore, that the increased appetite in obesity may, in some cases, be the result of abnormal neural or humoral influences arising in the soma. Carlson and Bulatao,[13] in 1924 showed that changes in the blood sugar level exert a pronounced effect upon appetite. It appears that the hypothalamus is sensitive to changes in the blood sugar level and possibly to other humoral influences as well.[14] The rare cases of obesity associated with islet tumor of the pancreas have suggested hyperinsulinism as a cause of common obesity, but it is well known that many cases of clinical hyperinsulinism are lean, while many diabetics are obese. Lowering of the blood sugar level, therefore, can hardly represent a force acting upon the hypothalamus in the production of common obesity.

Fat Storage

There remains in the pathogenesis of obesity the further possibility that, in the presence of a normally functioning hypothalamus and of normal humoral and neural influences operating upon it, an abnormally functioning fat storage mechanism could be the primary defect. This possibility has been considered by Wilder and Randall[15] who state:

"A factor possibly significant etiologically, in some cases of obesity, is that the fat stores are less available for oxidation while deposition of fat is accelerated (Bergmann). It is well known that the fat in lipomas is resistant to starvation; also that in lipodys-

trophy starvation causes a much greater loss from the thin upper half of the body than from the fat lower extremities. An analogous lipomatous tendency in general obesity, by withdrawing from circulation even a little more fat than usual, might well account for a delayed sense of satiety, much as the relative unavailability of the carbohydrate eaten by patients with uncontrolled diabetes gives rise to increased hunger (bulimia) of diabetes."

This hypothesis concerning the alteration of the appetite in the obese shares with all other theories of obesity a speculative status; its value, like that of the others, rests on the degree to which its fits the clinical and experimental facts of this condition. Known as the "lipophilia" theory, it has long been accepted by many European investigators as the most adequate explanation of obesity.[3c] In the American literature it was presented by J. Bauer in 1941.[16] While it has frequently been attacked since that time, there have been a number of recent developments which appear to strengthen its claims.

The following outline shows the relationship of this theory to the other theories of obesity which have been mentioned:

Theories of the Alteration of the Appetite in Obesity

1. Careless or perverted eating habits (Newburgh).
2. Altered sensitivity of the appetite-regulating center.
   a. Organic: Due to structural damage in the hypothalamus.
   b. Functional: Due to situations of stress, via the autonomic nervous system (Waife).
3. Alteration of humoral influences acting on the appetite-center.
   a. Organic: Islet tumor of the pancreas.
   b. Functional: Spontaneous hyperinsulinism.
4. Increased fat storage in the body—"lipophilia."
   a. Organic: Lipomatosis or lipodystrophy.
   b. Functional: A modern development of "lipophilia."

Regulation of Fat Storage

The concept of obesity as due to increased fat storage in the body presumes an active regulation of the size of the adipose deposits, rather than the mere passive response of these tissues to the balance between caloric intake and output. That the size of the adipose deposits responds to the balance between caloric intake and output is evident from experiments with overfeeding, caloric restriction, and variations in physical exercise. Weight can be gained or lost by these means. Such experiments, however, do not disprove the existence of an active regulatory mechanism which may be temporarily overwhelmed by the artificial conditions set up. An active regulation of the size of the adipose deposits was, like an active regulation of the appetite, first suggested by general principles of homeostasis. About 12 per cent of the weight of the normal body is adipose tissue.[17] After illness or starvation, in which the fat stores may be greatly reduced, there occurs a compensatory increase in appetite which prevails until the fat stores have regained their normal mass.[3d,18] In such a case there is discerned, in addition to a regulation of appetite to the energy needs of the body, a superimposed regulation of appetite, directed toward reestablishment of normal fat reserves. When these have been replenished the appetite levels off and the body weight remains constant. Nutrition experiments on animals have confirmed this common observation in human beings.[19] It is difficult to explain this phenomenon otherwise than by an active regulation of the size of the adipose deposits; and, if this occurs in the normal, it is possible that a derangement in the regulation of fat storage may account for some cases of obesity.

An older concept of lipophilia, in keeping with the prevailing opinion that the fatty tissues were relatively inert masses, assumed a qualitative difference between the adipose tissues of the obese and the lean. The fatty tissues, however, have been found to be metabolically very active.[20] Schoenheimer showed that the turnover of fat in these deposits is much more rapid than was previously sup-

posed.[21] Their size, therefore, depends on the rates at which fat is deposited in and mobilized from them. Wertheimer,[20] in a review of evidence indicating that mobilization and deposition of fat are controlled by neural and humoral mechanisms, concludes that the size of the adipose deposits is regulated by a dynamic equilibrium of forces. It is with this equilibrium that the modern concept of lipophilia is concerned.

It has been suggested, from considerations of the neural pathways, that alterations in the sensitivity of the hypothalamus may operate to produce obesity through an effect on the balance between fat deposition and mobilization, as well as through a direct effect upon the appetite.[17] In fact, among those who have been investigating hypothalamic obesity in experimental animals, there have arisen two schools of thought on the matter. Brobeck[8] believes the evidence favors the development of obesity by means of a direct effect upon the appetite, although he finds some data which do not fit in with this completely. Hetherington and Ranson[22] believe that the obesity is due, in part at least, to a decreased utilization of energy. Brooks, Marine and Lambert[23] found a lower metabolism in the animals after operation on the hypothalamus. They reported that: "As long as rats were held within certain weight bounds by limitation of food the total oxygen use remained below normal." they found, further, that with an equal intake of food, some of the operated animals accumulated more fat than the normal ones. These observations challenge the frequently encountered statement that lesions of the hypothalamus produce obseity exclusively by a simple and direct effect upon the appetite. They suggest, instead, that the hypothalamic lesions may affect the neural regulation of the mobilization of fat, as a result of which the general tissues would suffer a deprivation of nutriment. This could lead to a compensatory increase in appetite.

A retarded mobilization of fat has been found in the hereditary obesity of yellow mice.[24] In commenting on this, Brooks states:

"There can be no question as to the fact that obese rats can burn some fat because they lose weight when starved. There is reason to believe, however, that fat use may be impaired and several individuals have suggested this as one possible cause of obesity. Salcedo and Stetten fed labelled fatty acids and studied fat deposition and the rate of burning of depot fats in normal and obese mice. New formation of fat was not impaired in the obese animals but they did burn rather less quantities of depot fat. These investigators felt that the obesity might be attributed to the retarded catabolism of stored fatty acids."[25]

That an alteration in the regulation of fat storage accounts for some cases of human obesity is suggested by experiments on the respiratory metabolism. If the adipose deposits increase in size merely as a passive response to a positive energy balance, it would be expected that when the energy balance was changed in a negative direction they would again respond passively and give up their stores in an amount sufficient to maintain a normal energy output. The experiments of Strang[26] and of Ohlson,[27] however, show that, on subnutrition diets, the energy output of the obese declines significantly. The fatty deposits, though of excessive size, yield to the exigency of subnutrition with a reluctance similar to that of normal individuals undergoing semistarvation. The organism conserves its energy, though it has plenty to spare. This seems to be very strong evidence for an alteration in the mechanism of fat storage, rather than simple overfeeding, as a cause of obesity in the human.

Role of Pyruvic Acid

The recent discovery of the effects of pyruvic acid as a metabolic regulator in the tissues opens up a new development of the lipophilia concept which may have very practical applications in the treatment of obesity. Pyruvic acid, which is formed as an intermediary product in the breakdown of carbohydrate, inhibits the oxidation of fat[28] and stimulates the synthesis of fatty acids from smaller elements.[29] Significantly, too, pyruvic acid is an intermediary product in the conversion of carbohydrate to fat.[30] If, as suggested by Godlowski,[31] an enzyme block occurs at the pyruvic acid level of carbohydrate breakdown, it would follow that there would be more of this substance exerting its effects as a metabolic regulator in the tissues. If such is a cause of

obesity, we would expect to find in the obese a higher than normal blood level of pyruvic acid and of lactic acid, its product by reduction. Kugelman[3e] found an increased lactic acid level in obese subjects after light muscle exercise; and Prodger and Dennig[32] confirmed this in experiments which took account of the well-known effect of obesity in increasing the energy expenditure for a given task. There appears to be some evidence, therefore, for a defect in the oxidation of carbohydrate as a cause of obesity, as suggested by Von Noorden in 1907.[33]

The application of this concept to the treatment of obesity would be the very simple one of restricting carbohydrate severely in the diet. If this were done, less pyruvic acid would be formed. A defect in oxidation of this substance would then be of little importance, for there would be little of it exerting its influence as a metabolic regulator in the tissues, stimulating fat formation and inhibiting fat oxidation. Fatty acids in increased amounts would be withdrawn from the blood stream for oxidation in the tissues and their place taken by fatty acids mobilized from the adipose deposits.[34]

Low Carbohydrate Diets

Certain experimental and clinical observations suggest that this concept of obesity offers a method of treatment alternate to the usual one of caloric restriction. In 1928, at the Russell Sage Institute, three men lost some weight on an *ad libitum* intake of lean and fat meat, deriving about 80 per cent of the calories of the diet from fat and only 1 to 2 per cent from carbohydrate.[35,36] A similar diet has been used in a group of industrially employed people during the past three years[37,38] and, although most of them showed much greater degrees of obesity than did the subjects of the Russell Sage experiment, they too lost weight effectively without any restriction of their total caloric intake. In most cases it was found that a small portion of one of the less concentrated carbohydrate foods could be taken at each of the three meals of the day without interfering with weight loss. When normal weight was achieved it was maintained without qualitative change in the diet. The subjects of the Russell Sage experiment lost weight on an intake of over 2000 calories a day and maintained the loss on an intake which ranged up to 3100 calories a day. They showed an increase of 5 to 7 per cent in basal metabolic rate during the period of weight loss.

Therapeutic Implications

In the treatment of obesity, the aim of which is to reduce the size of the adipose deposits, it is axiomatic that the caloric expenditure must exceed the intake; and the most feasible way of accomplishing this has usually seemed to be by caloric restriction. This would be the ideal treatment if it were certain that the regulation of appetite had its basis only in habit or custom, and if it were certain, also, that the regulation of fat storage in the body were a purely passive process. The evidence for a homeostatic regulation of appetite and for an active regulation of the size of the adipose deposits, however, seems too strong to be easily brushed aside.

If the concept of obesity as due to excessive fat storage is the correct one, caloric restriction must be looked upon as merely nonspecific therapy, which reduces the weight of anyone, obese or lean, regardless of metabolic status, by opposing the homeostatic mechanism for maintaining energy balance. A more rational form of treatment, then, would be one which would enable the organism to establish a homeostatic equilibrium between caloric intake and expenditure at a normal level of body weight. In such a case, treatment would be directed primarily toward mobilization of the adipose deposits, and the appetite would be allowed to regulate the intake of food needed to supplement the mobilized fat in fulfilling the energy needs of the body. The use of a diet allowing an *ad libitum* intake of protein and fat and restricting only carbohydrate appears to meet the qualifications of such a treatment. This tends to support the validity of the "lipophilia" concept, in preference to the "simple overfeeding" concept of the etiology of obesity, and particularly so in view of the great liking for fat which, nutrition experi-

ments[6c] and clinical observations show, develops when carbohydrate is restricted in the diet.

Summary

Evidence for a homeostatic regulation of the appetite and of fat storage suggests, as a cause of obesity, some other hypothesis than "simple overfeeding." Two hypotheses are discussed. These are (1) psychic stress operating through the autonomic nervous system on the hypothalamus, and (2) the "lipophilia" concept of obesity. The type of treatment to which each of these concepts of obesity leads is indicated.

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Resumen

Una nueva hipótesis sobre el problema de la obesidad

Evidencia de una regulación homeostática del apetito y de los depósitos de grasa sugiere como causa de la obesidad una hipótesis que no sea simplemente la de la "sobrealimentación."

Se discuten dos hipótesis: (1) tensión psíquica actuando mediante el sistema nervioso autónomo sobre el hipotálamo, y (2) el concepto "lipofílico" de la obesidad.

El tipo de tratamiento sugerido por cada uno de estos conceptos de la obesidad está indicado.

CALORIC VALUES FOR COMMON "SNACK" FOODS

"JUST A LITTLE SANDWICH"	Amount or Average Serving	Calorie Count
Hamburger on bun	3" patty	500
Peanut butter	2 tablespoonfuls P.B.	370
Cheese	1½ oz. cheese	400
Ham	1½ oz. ham	350
BEVERAGES		
Carbonated drinks, soda, root beer, etc.	6 oz. glass	80
Cola beverages	12 oz. glass (Pepsi)	150
Club Soda	8 oz. glass	5
Chocolate Malted Milk	10 oz. glass (1¾ cups)	450
Ginger Ale	6 oz. glass	60
Tea or coffee, straight	1 cup	0
Tea or coffee, with 2 tablespoonfuls cream and 2 teaspoonfuls sugar	1 cup	90
ALCOHOLIC DRINKS		
1 Ale	8 oz. glass	130
1 Beer	8 oz. glass	110
1 High Ball (with ginger ale—ladies' style)	8 oz. glass	140
1 Manhattan	Average	175
1 Martini	Average	160
1 Old Fashioned	Average	150
1 Sherry	2 oz. glass	60
Scotch, bourbon, rye	1 oz. jigger	80
FRUITS		
Apple	1 3-inch	90
Banana	1 6-inch	100
Grapes	30 medium	75
Orange	1 2¾-inch	80
Pear	1	100
SALTED NUTS		
Almonds	10	130
Cashews	10	60
Peanuts	10	60
Pecans	10 halves	150

(Courtesy of Smith, Kline & French Laboratories, Philadelphia)

SEMISTARVATION and NUTRITIONAL REHABILITATION

A Qualitative Case Study, with Emphasis on Behavior

By JOSEF BROŽEK, PH.D.

INTRODUCTION

IN THE PRELIMINARY communications[1,2] and in the comprehensive report[3] on the semistarvation-rehabilitation experiment carried out at the University of Minnesota in 1944–45, the case studies were limited to the psychological aspects, with emphasis on *severe* manifestations of "semistarvation neurosis." The present study, broader in scope and including other data in addition to those directly related to behavior, is concerned with a subject who in many respects was fairly typical of the group as a whole. The semistarvation changes in the quantitative characteristics, described in detail in a separate report, were frequently very close to or identical with the average changes obtained for the group as a whole.[4]

The details of the dietary regimen and the general living arrangements were described elsewhere.[3] Suffice it to say here that after 12 weeks of the control period, with an average daily intake of 3870 cal., the subject's intake was abruptly reduced to 1660 cal. The average caloric intake for 24 weeks of semistarvation was 1470 cal. During rehabilitation the intake was increased to 1780 cal. for the first 6 weeks, to 2550 cal. for the 7th to 10th week, and 2840 cal. for the last 2 weeks of the controlled diet. The average intake for the following 8 weeks of unrestricted food intake was 4740 cal.

In the basal starvation diet, modified in individual cases by increasing or reducing the bread and potato ration, protein, fat, and carbohydrate contributed 12.5, 18.2, and 69.3 per cent of the calories, respectively. In contrast to the control diet, there was a reduction in the percentage of calories derived from fat (37.0 vs. 18.2) and an increase in calories derived from carbohydrate (50.0 vs. 69.3 per cent). The relative amount of protein was essentially unchanged. In terms of individual foodstuffs the experimental diet was designed to approximate the type of foods likely to be available in European famine areas. No limit was placed on salt intake. With reference to the vitamin content, the basal semistarvation diet contained 1600 I. U. of vitamin A, 1.3 mg. of thiamine, 0.6 mg. of riboflavin, 21 mg. of niacin, and 83 mg. of vitamin C. During the period of controlled rehabilitation the diet was increased in volume, without essential changes in its composition.

The chronology of the experiment is given in Table I.

TABLE I

Chronology of the Experiment

Control period	12 weeks (C)
Semistarvation	24 weeks (S 1 to S 24)
Restricted rehabilitation	12 weeks (R 1 to R 12)
Unrestricted food intake	8 weeks (R 13 to R 20)
Follow-up testing	at R 33

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis.

Presented at the Meeting of the Ohio Dietetic Association, Akron, Ohio, on April 26, 1952.

The support for this work was derived from a variety of sources[3] (p. xxvii).

Personal Background

The subject (No. 123 in our records), whom we shall call Don, was 25 years of age at the start of the experiment. He was a tall fellow (181.0 cm.), moderately underweight with reference to the age-height-weight standards, highly intelligent, with "normal" personality characteristics—both clinically and psychometrically. He was well liked by the other subjects and the staff. The author had frequent opportunities to deal with him as a supervisor of his clerical work.

After graduation from an Institute of Technology with a major in architecture, Don was apprenticed to an architectural firm up to the time he was inducted into Civilian Public Service. His deep religious motivation and sincere altruism were clearly reflected in his conduct and in his personal and social attitudes. He welcomed the opportunity to serve in a nutritional experiment that promised to yield information necessary for coping with the effects of semistarvation, widespread in the war-torn world. His social concern also found expression in his desire to participate in relief and rehabilitation work abroad when the hostilities would end. For this purpose he was willing to relegate temporarily the resumption of his architectural career to second place.

There were strong ties of mutual affection between the subject, his parents, and his sister. The family approved of his position as a conscientious objector and they were happy to have him serve in a Civilian Public Service project. Appraisal of extensive biographical material and his behavior during the control period indicated effective and mature adjustment. The subject was personally attractive, interesting, and congenial. There was nothing unusual or striking in his medical history.

Physical Appearance and Status

The profound changes in Don's physique during the period of starvation and subsequent nutritional rehabilitation are clearly indicated in the photographs (see Fig. 1). The body weight during the control period was 64.7 kg. (142 lb.), after 12 weeks of semistarvation 55.8 kg. (123 lb.), and after 24 weeks of semistarvation 52.1 kg. (115 lb.), with a weight decrement amounting to 19.5 per cent of the control value. In rehabilitation the weight increased to 54.2, 68.9, and 74.1 kg. after 12, 20, and 33 weeks, respectively.

At S 24 the reduction of soft tissues, including both the subcutaneous fat and the musculature, was marked all over the body. The cheekbones became prominent; the face and the neck (especially in the dorsal view of the subject) were thin; the collar bones, the vertebrae, the ribs, and the scapulae stood out; the arms and the legs were spindly, and the loss of tissue resulted in a large space between the thighs; the fat padding disappeared, leaving the chest area and the area of the buttocks flat. During rehabilitation these changes were reversed, with the subcutaneous fat showing a marked increase. Even though at this time the subject's weight was not excessive, he appeared obese.

The changes in body build, described in terms of Sheldon's somatotype components, are presented in Table II. The ratings, based on photographs, were made independently by Dr. Gabriel Lasker of Wayne University and by a group of workers at the Harvard Anthropometric Laboratory, under the supervision of Dr. James M. Andrews, IV. At Harvard, each pair of photographs, rated without making direct comparisons of the pictures taken during the control period (C) and after 24 weeks of semistarvation (S 24), was somatotyped by 3 or 4 different observers. The tabular values are averages of the individual ratings.

TABLE II

Changes in the Somatotype after 24 Weeks of Semistarvation

Somatotype Component/ Rater	Endomorphy		Mesomorphy		Ectomorphy	
	C	S 24	C	S 24	C	S 24
G. Lasker	2	1	5	3	3	5
Harvard Group	3	2	4	2	3	6

In Dupertuis' descriptive terms, the three "components" of a somatotype correspond to soft roundness (endomorphy), muscular solidity (mesomorphy), and linearity-delicacy (ectomorphy). Each component is rated on a scale varying from 1 (very low) through 4

(intermediate) to 7 (very high). Although the two sets of ratings (see Table II) differ somewhat, the trend of changes is reflected consistently in both sets. There is a decrease in endomorphy and mesomorphy, while ectomorphy ratings markedly increase. For detailed discussion of methods and average trends see Lasker's report.[5]

A detailed clinical examination at the end of the starvation period was carried out by Dr. Russell M. Wilder of the Mayo Clinic. He noted the emaciated appearance of the patient, including the winged scapulae, deep suprasternal notch, prominent rib cage, and pipestem arms. The skin appeared sallow, dry and roughened. When it was picked up between the fingers it felt thin and inelastic, resembling in these qualities the skin of an old man. There were some irregular splotches of brownish pigmentation in the infra-orbital area. The hands felt cold to the examiner's touch but were not sweating. The fingernails were atrophic, showing evidence that the subject was biting his nails. There was definite Grade I cyanosis of the nail beds and there was question as to whether the lips weren't also blue. Otherwise, no disease of eyes or mouth was noted. The patellar and ankle reflexes appeared to be "normal," with good vibration sense in the tibia. There was definite weakness of the quadriceps femoris muscles as indicated by the difficulty experienced in rising from a squat. Grade I pitting edema was noted over the shins and ankles.

Don differed from some of the other subjects in that he did not have the dull appearing eyeballs with a sclera resembling unglazed white porcelain. No "permanent gooseflesh" was noted, although this was common, especially on the exterior surfaces of the upper arms and legs of many of his fellow subjects. Don's lips were not cracked, nor was there thinning of the epithelium and maceration at the angles of the mouth. These findings, which were common among the group as a whole, were judged not to be true angular stomatitis and cheilosis. Finally, depressed or absent patellar and ankle reflexes were common findings in the group as a whole.

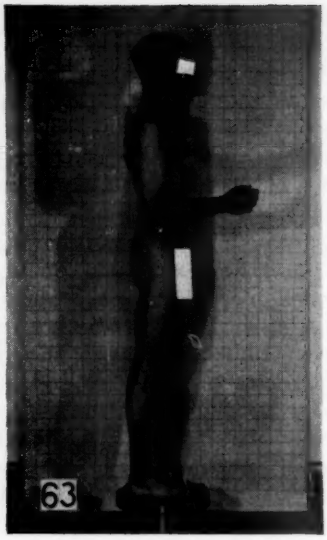
Don's basal pulse was slow and weak but very regular. The heart sounds were faint and distant and his heart was not enlarged when examined by percussion. He exhibited no dyspnea on exertion. The details of the objective measurements in Don have been presented elsewhere[4] but it may be mentioned here that his basal metabolic rate was markedly reduced, as was the circulating hemoglobin. He exhibited a trivial decline in serum protein concentration. His blood sugar was slightly below normal, especially during physical work. The nitrogen excretion was reduced to almost one-half of the control level, while the urine volume was more than doubled. The component of the total energy expenditure, corresponding to "physical activity" was reduced to one-quarter of the initial value. Among the components of motor fitness (strength, speed, coordination, endurance) endurance showed the most drastic deterioration, the kilogrammeters of work performed in running on an inclined treadmill decreasing to less than one-tenth at the end of the semistarvation period.

Ratings of Adjustment

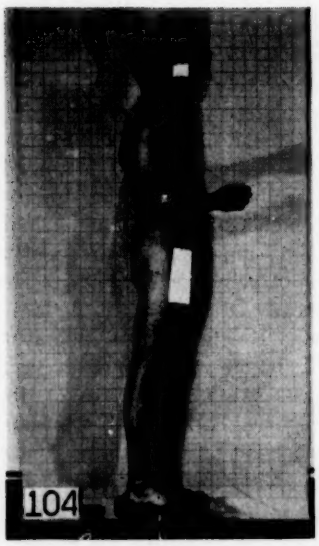
In a standardized Complaint Inventory, consisting of 55 items, Don marked only one item in the control period, 14 at the end of starvation, 8 at R 12, and 3 at R 20. The average increment of complaints was 14 in the group as a whole. At the end of 24 weeks of semistarvation Don noted that his mood fluctuated without any particular reason. The "guinea pig" life seemed to be a strain for him much of the time. He tired quickly, and frequently had the sensation of being weak all over. He felt clumsy, unsteady, and uncertain of footing when walking. He thought his judgment was not as good as before and he found it hard to keep his mind on any particular task. His work capacity, physical and mental, was substantially lowered. He felt more like giving up when things went wrong than before. He felt hungry much of the time.

A series of symptoms was rated by the subject on a scale from normal (0) to extremely abnormal (± 5). The principal items and Don's ratings of them are reproduced in Table III. There was a pronounced increase in the

C

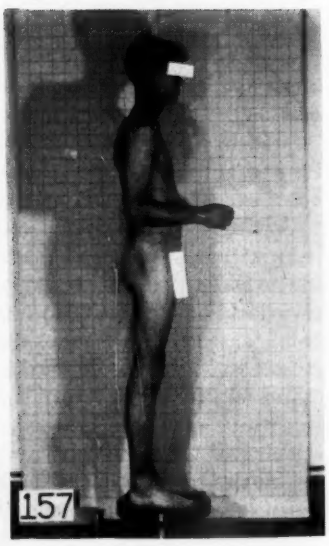


S 12



S 24

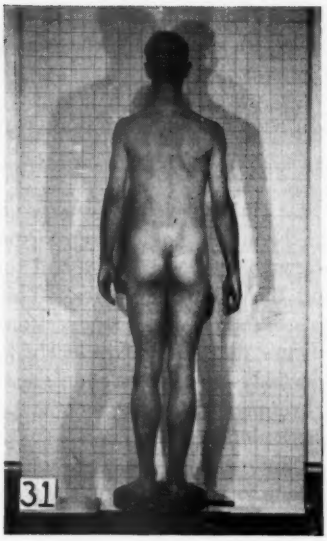
R 12



R 20

Figure 1

Don's physical appearance at different stages of the starvation-rehabilitation experiment: side view.



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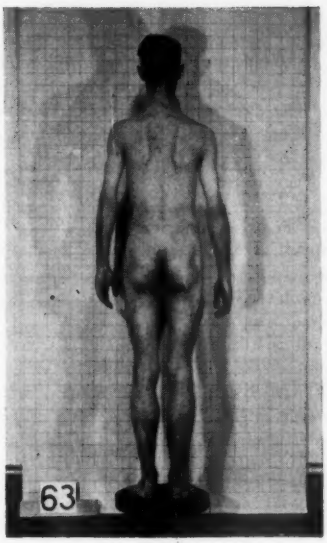
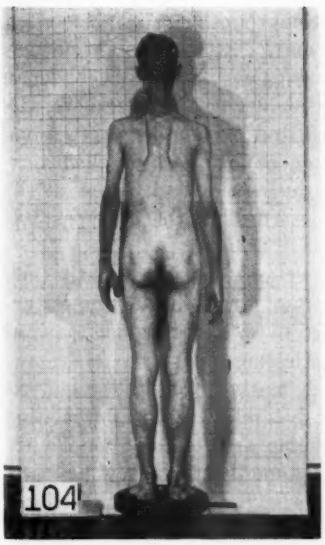
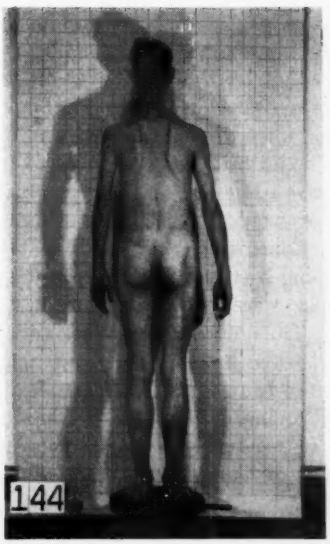


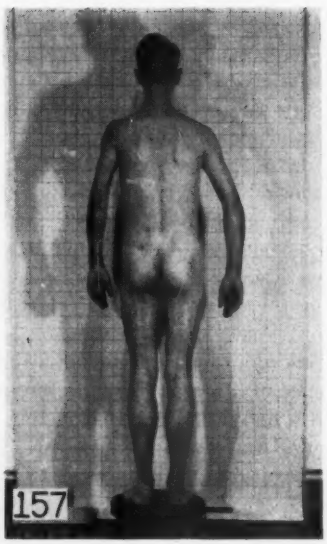
S 12



S 24



R 12



R 20

Figure 1

Don's physical appearance at different stages of the starvation-rehabilitation experiment: back view.

TABLE III

Symptoms of Semistarvation Deterioration, the Intensity of Which Was Rated by Don on a 5-point Scale (0 = Normal, +5 or −5 = Extremely Abnormal). The Control Values Are 0 ("Normal") and Were Omitted from the Table

	Week of Semistarvation	
	S 12	S 24
Desire for Food ("appetite")	3	3
Dizziness	2	1
Tiredness	3	3
Muscle soreness	2	2
Depression	1	1
Moodiness	1	1
Irritability	2	1
Apathy	2	1
Self-discipline	−1	−1
Mental alertness	−1	−1
Ability to concentrate	−1	−1

desire for food and in tiredness. Muscle soreness, dizziness, apathy combined with irritability came next. Don recorded some depression and moodiness, and a decrement in self-discipline, mental alertness, and in the ability to concentrate. It is in keeping with his character that Don's ratings, in comparison with results of direct observation and other sources of information, are conservative estimates of the changes that had taken place.

The tendency to underestimate the magnitude of the alterations brought about by the starvation diet was particularly marked in his graphic ratings of three "drives"—the drive for food, for activity, and sex. The latter two showed in reality a striking decrease while according to Don's ratings the changes would appear negligible. Some of the symptoms which were noted in the diary and will be discussed in the next section of this paper were not brought out in the ratings at all. Thus he recorded no change in "ambition." The presence of "hunger pain," differentiated from the less definitely localized feeling of "being hungry," was rated positively (+1) only in mid-starvation (S 12); this is true also of nausea and sensitivity to noise. After 12 weeks of controlled nutritional rehabilitation (R 12) most of the items were rated "normal," while in fact he was far from having completely recovered. His independent estimates of the over-all recovery (with values of 25 per cent at R 6, 60 per cent at R 12, and 90 per cent at R 20) reflected more truly the real state of affairs.

Behavior during Semistarvation

Interviews and Diaries

Don was interviewed regularly by Mr. Joseph C. Franklin, one of the assistant psychologists, who prepared a digest of the interviews and the subject's diaries. This digest served as a basis for subsequent sections of this paper. Don's diary was excellently kept but was somewhat superfluously detailed. This was in keeping with his general tendency toward meticulousness.

The first interview in the semistarvation period was held with Don during the third week (S 3), at a time when he had lost about 10 lb. of weight. He did not appear greatly affected by the reduction of food intake. In fact, he reported feeling *more* interest in his architectural pursuits. This was a pleasant surprise to him. He was rarely conscious of hunger, but he did experience some stomach pains and cramps. The "drive" to motor activity showed some signs of falling off, with an increase in fatigability, yet much of the time Don felt completely "normal." From the point of view of over-all adjustment, the subject made an excellent impression during the interview. His morale was high and accomplishments along the lines of his endeavors were excellent.

His condition during the week following the interview was described in the diary as follows:

Food: "Hunger sensations up slightly during the early part of week, marked on Saturday, accompanied by weakness in legs, general tiredness, and listlessness."

Creativity: "Creative urge still high, expressed in work in architectural appreciation class, some designing (architectural) on Thursday and Friday, some sketching on Friday."

Activities Drive: "Spirits high on Wednesday, Thursday, Friday. Mental energy unimpaired—physical drive gradually decreasing. Physical drive sharply reduced on Saturday; walk neither anticipated nor enjoyed and its pace considerably slowed down. Men-

tal energy this day somewhat reduced, tired and lethargic; morale slightly affected; quite subject to blackouts when rising suddenly."

At the next interview (S 8), the subject's weight had fallen to 127 pounds (initial value 142 lb.). He reported that he felt just about an "average" impact of the semistarvation stress, in comparison with the other men. His health had been good during the month except for a cold lingering longer than usual. Hunger had become a "passive experience" for him. He noticed it only when the routine eating schedule was upset. He had had no dreams of food. Although he occasionally thought about food, he was in no way preoccupied with food thoughts or phantasies. The "bull sessions" of his fellow-subjects disturbed him because conversations inevitably got bogged down in discussions of diet and food.

There was no indication of mental impairment. He was as much "on the ball" as ever. He wrote, on the average, six or seven letters a week ("normal"), audited a course in Social Pathology, studied French, and had assumed leadership in planning a relief and rehabilitation course to be provided for the group. He expressed disappointment that the plans were retarded because others had not taken their responsibilities as seriously and enthusiastically as he did. He stressed the lift provided for his architectural studies by his vivid imagery and aesthetic experiences. He felt that he had been increasingly sensitive to color, form, and texture since the beginning of semistarvation.

He characterized the group of his fellow subjects as "more sober, a bit more irritable, and more petty than had formerly been the case." During this week (S 8) the subject recorded a dream, the first since the beginning of starvation which had concerned food: "People and place not clear; all apparently eating pancakes and syrup (a favorite of mine) and chocolate bars (had seen one passed among overhead personnel during the preceding afternoon). Others apparently subjected to experiment like myself, but they ate without the uneasiness which I felt. Quite suddenly, without clear cause, something caused all to place in a receptacle passed around the portions of their pancakes which remained uneaten. At this point, all entered cars and drove from the scene. Remorse felt by myself because of the knowledge that I had known myself to be doing something wrong while in process of doing it; end of dream, wakefulness, great relief. . . ."

At the next interview (S 12), the subject exhibited and reported a wide range of stress-marked behavioral changes. Specific food cravings had developed. Additional dreams about food and eating were noted. On one occasion he dreamed that he had broken the diet. He reported the return of fingernail biting as a nervous habit. Walking, a prescribed physical exercise, was associated with aches and pains. He experienced muscle cramps both while resting and after exercise. Loss of sex drive was marked. "Sex is dull mud," he commented. Hunger was heightened and he attempted to counterbalance it by increased gum chewing. Hearing had become disturbed by what he described as "sensations of fullness in ears, echoing, and double sounds." Dizziness upon arising from lying or sitting positions and even when active had become prominent.

The subject described himself as restless, more irritable than ever, with annoyances becoming less momentary and fleeting than before. He had grown more impatient at having to be introspective regarding his condition, e.g. keeping the required diary. Apathy had increased. Capacity for concentration either in thinking or pursuing given activities was reduced; he complained that he found himself continually wandering from interest to interest. Self-confidence had markedly declined to the point where he welcomed more and more laboratory control and stated: "I think it is a good idea to put strong checks on us."

The diary vividly fills in the details supporting generalizations and statements made during his interview. He commented: "Noticed occasionally a tendency toward carelessness in matters of personal health and appearance; temptation arises to pass up a shower, to skip or postpone shaving, to slight or hurry tooth brushing, to wear old clothes on campus

or to town, to put off all mending, darning, and button sewing. Have noticed the elements of pettiness, aggressive and insistent argument, hesitant and inexact speech, sloppy thinking on occasion in myself and others with the result that I have temporarily, at least, lost rapport with some members of the unit. Have noticed an increased satisfaction in being alone, a further drop in desire for social gatherings and group activities. Being so much aware of my hunger and my weakness, I seem to detect a general turning of my attention to myself, to my concerns, problems, moods, likes and dislikes, thoughts, interests, wishes, etc. I am perhaps less interested in others, more impatient with them; interest in relief and rehabilitation seems to be shifting radically to an exclusive interest in architecture, rural or small community life, a personal home life. . . . Contrary to my earlier attitude, when I feared time was passing too swiftly to permit the accomplishing of all I had set before myself to do by November, I now quite definitely am looking ahead with pleasure to the end of the experiment. Not homesick in the usual sense, I nonetheless find my thoughts often turning toward home, the quiet life there in the family circle, to plans to return to the farm on furlough, to cooking my meals there, to quiet mornings of study, to afternoons of physical labor on the farm. . . . It seems that the strain of life, though by no means intolerable or unduly oppressive as yet, is definitely increasing. . . ."

By S 16 Don's weight had gone down to 119 pounds. He reported the persistence of most of the symptoms and complaints already described. However, some changes were noted: dizziness decreased; hunger, in general, had diminished but when pangs occurred the pain exceeded anything previously experienced; nocturia had become commonplace; severity of cramps (especially in the calves of the legs, ankles, and feet) increased; back and shoulder aches became more definitely associated with physical exertion. The subject had had six severe headaches during this period; and he occasionally found his vision at night to be blurred.

The general picture at this point was one of markedly reduced activity, mental depression, and lassitude. The good feeling and humor which characterized his normal behavior was almost entirely gone. The subject was ambivalent about food and the activities with which it was associated. He resented the hold, the compelling nature of his deprivation and struggled to deny the sway which so purely an "animal" drive could exert over his life. Yet he was inevitably drawn toward food and discussions of food. Both to create a sensation of fullness in the stomach and to obtain the "lift" caffeine was observed to provide generally, he consumed up to four glasses of water per day plus some nine cups of black coffee and/or tea per day. The subject pointed out that weather and climatic conditions had come to have an important influence on his morale. About this time his interests had undergo a radical change. The egocentric effects of the semistarvation, added to a new realization of the importance of personal security, led to dropping of all relief study and training.

In the middle of June (S 18) his girl friend had come from the East to spend a week visiting the subject. He described this visit as a considerable strain and felt that it had been impossible for him to achieve rapport with her.

The interview held at S 20 revealed that the psychobiological symptoms of stress continued pretty much as the subject reported them at the end of May (S 16), except that elements of indecision and uncertainty became more dominant. He had a strong feeling that "the experiment cannot conclude too soon," while, on the other hand, he expressed a desire to remain for the post-rehabilitation experimental period.

The subject's weight at the time of the next interview (S 22) was 115 pounds. He experienced a marked resurgence of hunger and hunger pains, and a greater weakness in the legs than ever before. Frequently his knees would "buckle under" when walking; treadmill walking had grown increasingly difficult—"almost impossible at times." Activity was down to a new low. He stated that most of his time was spent "just sitting." Much of the

time he went over his files and worked on his scrapbook. No longer was he able to keep up his studies, although he continued to accompany another fellow, as a "buddy," to two classes.* More than ever, he voluntarily confined himself to the Stadium and Laboratory quarters, making fewer and fewer excursions other than those required by the prescribed quotas of outside walking. Recreation became largely restricted to passive pursuits. He attributed his weight fluctuations to edema which became pronounced during June. Sleep requirements increased as he grew to be more and more tired, and frequently he felt exhausted early in the evening.

Regarding food, Don developed elaborate procedures for making concoctions designed to stretch to the utmost, by the addition of water, the food that was served to him. Moreover, he consistently drank the limit of nine cups of coffee and/or tea each day. Although he showed less interest in food and diet than many of the "guinea pigs," he became interested in the subject more than at any previous point in the experiment. He did not, as did many of the other subjects, spend time poring over recipes in cookbooks, yet he remarked that when he thumbed through magazines, pictures of food were most appealing. His cravings for special foods were largely focussed on meats—especially pork, ham, bacon, sausages, and the like.

Previous complaints about hearing difficulties were no longer present. Dreams, particularly food dreams, had become more frequent during this time. A dream two nights before the interview involved a huge pile of fresh bread, spread with butter and jam. He dreamed that he took a tremendous bite out of the bread, and then realized that he was on a starvation diet and spit it out.

At the last semistarvation interview (S 24), Don felt very "low." Edema had become pronounced in his legs, ankles, and face. He had several severe stomach-aches. Activity had reached an all-time low. He felt that he had almost no stamina and endurance left—"one-half hour of treadmill walking is almost more than I can manage." The subject confessed that recently he had exceeded his quota for coffee and saccharine. It had become difficult for him to restrain himself from buying books and other things which he realized would be of little use at the time and in the near future, and cited this as evidence of a loss of self-control. Reading, studying, and even letter writing had become difficult for him, with the result that he had all but given up these activities. He stated that one of the things that bothered him was his inability to get started, to initiate activity. The fact that he had experienced memory lapses reinforced his suspicions that he had mentally deteriorated. He felt that he could expect little of himself—"It's now a question of passing time until the end." Several times during the interview he reiterated the hope that in rehabilitation he would be placed in the highest of the four caloric groups.

Behavior during Rehabilitation (R 1–R 12)

In the rehabilitation period, the subject was placed in the lowest caloric group, with an intake of 1780 cal., as compared with 1490 cal. during the last week of semistarvation. After five days on the diet (R 1), the subject reported experiencing a surprising "general sense of well-being." He was enthusiastic, and commented that an "amazing improvement has occurred." In general, "hunger is down and activity is up, and weakness is decreased." The subject noted that he felt better than his physical condition appeared to warrant. The previous day he jumped up three steps, feeling frisky, but had a hard time to keep from collapsing because his legs buckled under him. He felt that he could undertake more activities and was optimistic about the future.

However, the "improvement" was definitely a temporary one. At the time of the next interview (R 3), the subject felt a definite "let down." "Things are not going as I had thought they might," he noted. Outside and treadmill walking still tired him out; he did not sleep well and woke up unrefreshed in the mornings. He was increasingly "anxious to

* At this time the subjects were allowed to go outside the Laboratory only in pairs.

get this thing over with." "Rehabilitation has been an unexpected stress. I do not feel that I am getting more to eat than I got on the semistarvation standard diet." The subject decided not to volunteer to stay at the Laboratory beyond R 12. The subject's reading was largely limited to devotional literature, and he described his sense of the "religious" as having risen over anything previously experienced. But the frustrations of his expectations of early rehabilitation and the continued hunger, which the diet failed to allay, colored his thinking. The subject bitterly complained of alleged mistakes in caloric bookkeeping. His ideas that he was getting less food than he was entitled to were becoming an obsession. Activity slumped again, and his condition had by and large reverted to that prevailing at the end of the semistarvation period. Letter writing (down to about three per month) and keeping his diary were accomplished only with the greatest effort.

The subject had failed to gain any weight over his semistarvation low point at the time of the next interview, almost two months after the beginning of the rehabilitation diet. Nevertheless, he reported, "there have been times when I had a sense of strength and general well-being." Although, in general, the feeling of hunger had been somewhat reduced, he reported a vigorous reassertion of the hunger drive during the preceding week. He engaged in no more activity than was absolutely necessary, occupying his time by going over his files, reading, and sorting and disposing of the store of "stuff" he had collected during his period of acquisitiveness. He evidenced no desire to participate in group functions.

Tiredness was evident to a considerable degree, but he described it as of "a more normal kind rather than the utterly poohed-out feeling" he used to experience during semistarvation. He continued to require what he considered as excessive amounts of sleep, and during a cold spell he found it difficult to keep comfortably warm. Even though sex drive had recuperated to some extent, he had had no sex dreams and didn't crave feminine companionship. With the passage of time the religious and devotional interests became less prominent, having been partly replaced by the concern with field work in relief and rehabilitation at the community level in the United States. The interest in foreign rehabilitation and relief work had all but disappeared. He was not happy about having been selected to remain at the Laboratory as a "guinea pig" until R 20, and accepted this responsibility only out of a sense of duty.

During the latter part of the semistarvation period the subject developed food and eating habits which were annoying to many of the other subjects. These patterns of behavior became still more bizarre during the rehabilitation period and included keeping food hot by piling it up on toasters, adulteration of food served by adding to it water and spices, and making weird concoctions and peculiar mixtures. This was at a time when the food and eating habits of most of the men were on the up-grade. Despite attempts to be tolerant, other subjects could not suppress severe criticism of his meal-time behavior. The subject was aware of this but claimed that all attempts to modify these dilatory and ritualistic habits had been unsuccessful. He refused to be high-pressured by men who in most cases were getting considerably more food than he did.

Approximately a month later (R 12), toward the end of the increased but controlled diet (2840 cal. per day), the subject reported that his psychological and physiological condition was improving. However, the recovery was far from being complete. He had gained only seven pounds over his semistarvation weight and dwelt upon the ways in which he was not yet rehabilitated: "I still get too hungry too often. I have weakness in my legs. Psychologically, these things come and go—irritability, feelings of being worn out, unsureness of myself. I have the feeling that I am flitting about on the surface of things; I have less self-discipline and confidence. I am susceptible to undue tiredness. I need more than normal amounts of sleep."

The subject was more reconciled to remaining at the Laboratory for another eight weeks, until December, and said that he appreciated

the opportunity for further rehabilitation before seeing his family and friends. He felt that there had occurred much improvement in his eating and food habits, but regarded his sex drive as hardly improved at all. His interests by now had shifted to low-cost housing, rural housing, and small community planning. The importance of attaining physical security had been sharply focussed by his semistarvation experience. He declared that he had given up plans to do relief work abroad because "it is more important to get established." When demobilized, he planned to finish his apprenticeship, obtain a license as an architect, and get started on his own.

Behavior during the Terminal Period (Unrestricted Food Intake, R 13–R 20)

During this period the subjects ate in a student cafeteria and no restrictions were placed on the foods and amounts they chose to eat. The caloric intake rose precipitously, reaching over 6000 cal. per day during R 15 and returning to less than 4000 at R 20.

During R 13 the subject's weight had increased to 125 pounds. He reported that although he occasionally wiped his dishes clean with bread (no longer with fingers or tongue), his eating manners had much improved. No longer did he "dawdle" interminably over his food. Over the week-ends, when the subjects were permitted to eat whatever and as much of it as they wanted, not being limited to the University cafeteria menu, the subject experienced an irresistible tendency to overeat. He recorded the following complaints attributed to excessive food intake: stomach pains, "gas," belching, some nausea, sleepiness during the day, and persistent headaches. Strangely enough, his "appetite" for food was unsatisfied even when he ate until he was uncomfortably full. Food, nevertheless, had grown to be a much less exclusive concern. He reported marked improvement in the activity drive and the capacity for physical work, and had been able to saw and haul wood for two hours on one occasion before tiring. There remained a heightened appreciation of the importance of food, but it became more socially oriented. Don became more sharply aware of the necessity of providing adequate diets for people everywhere than he was before the experiment.

According to the subject's report for R 16, when his weight had gone up to 142 pounds, he had much improved in most respects, except for the slow return of full strength and endurance. No specific food cravings were indicated, but the subject stated that he preferred simple to rich or sweet foods. Eating habits returned to normal. Sex drive was reported as fully recovered.

Ability to do hard physical work was reported as rapidly approaching normal at R 20, but he still experienced some difficulty in lifting and climbing. At this time the subject's weight was 152 pounds and he regarded his recovery as practically complete.

Comment

Don's case history is of more than passing interest. It reflects well the general type and magnitude of alterations observed in the group of 32 volunteers for the semistarvation-rehabilitation experiment. The changes in many of his quantitative characteristics were close or identical with the group means.

During the long 24 weeks of the semistarvation period, the changes — both in his physique and in his behavior—were proceeding slowly, almost imperceptibly. It is only when they are telescoped in time, e.g. by the simultaneous consideration of the pictures obtained during the control period and after 24 weeks of semistarvation, that the magnitude of differences becomes fully apparent. Much the same was true of the behavioral aspects of semistarvation deterioration. In the control period we had before us a pleasant, cheerful, active young man, full of initiative, cooperative and sociable, highly altruistic, sensitive to the world's social problems, and eager to play his part in the rehabilitation of the war-torn world. Twenty-four weeks later there remains only the shadow of Don's former self. Weak and edematous, lacking physical endurance and mental initiative, grouchy and self-centered, without interest in female companionship, he was a childish slave of food, primarily concerned with individual security rather than with the larger

issues of repairing the damage done in so many parts of the world by war and by the undernutrition which bordered on starvation.

The contrast is striking and frightening. The development of "semistarvation neurosis" can be traced directly to the prolonged caloric deficiency and the resulting physical deterioration. The psychological pressures and frustrations inherent in the experimental situation must have colored, but have not basically altered, the somatopsychological etiology of the profound changes in Don's overt behavior and personality. It was through nutritional rehabilitation that these changes have receded and that—slowly, at first, but definitely—a recovery in the physical and the psychological area took place. Thirty-three weeks after the end of the semistarvation period Don was largely back to the prestarvation "normal," except for a somewhat less cheerful outlook and elevated concern regarding matters of health.

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Resumen

Semi-inanición y rehabilitación nutritiva: Un caso cualitativo.

El caso del joven aquí estudiado ("Don") es de un interés más que pasajero. Refleja bien el tipo general y la magnitud de las alteraciones observadas en el grupo de 32 voluntarios sometidos a la experiencia de semi-inanición y rehabilitación nutritiva. Los cambios en muchas de sus características cuantitativas eran muy semejantes o idénticas a los promedios del grupo.

Durante las 24 lentas semanas del período de semi-inanición, las alteraciones—tanto físicas como de su comportamiento—procedían lentamente, casi imperceptiblemente. Sólo cuando se las comprime telescópicamente en el tiempo—eso es, por la consideración simultanea de los cuadros obtenidos durante el período control y después de las 24 semanas de semi-inanición—aparece en su plenitud la magnitud de las diferencias. Lo mismo, más o menos, puede decirse de los aspectos de su comportamiento, influido por la deterioración resultante de la semi-inanición. En el período control, teníamos ante nuestros ojos a un joven simpático, alegre, activo, sociable, dotado de iniciativa y cooperación, sensible a los problemas sociales del mundo, y ansioso de jugar su papel en la rehabilitación de un mundo trastornado por la guerra. Veinte-cuatro meses más tarde, sólo queda la sombra del "Don" anterior. Debilitado y edematoso, sin perseverancia física e iniciativa mental, quejicoso y egoïsta, indiferente a las mujeres, esclavo pueril de los alimentos, preocupado más bien por su propia seguridad que no por los problemas mas amplios de la reparición de los daños hechos en tantas regiones del mundo por la guerra y por la malnutrición rayando con la inanición.

El contraste es notable y espantoso. El desarrollo de la "neurosis de semi-inanición" es facilmente trazable a la deficiencia calórica prolongada y la deterioración física de ahí resultante. Las presiones y frustraciones físicas inherentes en la situación experimental habrán colorado, pero sin alterar básicamente, la etiología somatopsicológica de las profundas alteraciones en el comportamiento patente y en la personalidad de Don. Ha sido por la rehabilitación nutritiva por la que estos cambios se han revertido y que—lentamente al principio, pero de modo definitivo—se ha producido la recuperación física y psicológica. Treinta-y-tres semanas después del fín del período de semi-inanición, "Don" se hallaba mas o menos restaurado al estado de "normalidad" que precedía a la semi-inanición—pero siempre con una actitud algo menos alegre y una preocupación accentuada por las cosas de su salud.

CLINICAL VITAMIN DEFICIENCIES *in patients with* DIABETES MELLITUS

By BARKLEY BEIDLEMAN, M.D.

VITAMIN DEFICIENCIES appearing clinically in patients with diabetes mellitus may be divided into two groups. The first group includes those deficiencies which appear in diabetics who are eating a diet low in total calories and fat for reduction of weight and prevention of atherosclerosis. These deficiencies are usually multiple and differ in no way from those occurring in non-diabetic patients under similar conditions of dietary deficiency. The second group includes those deficiencies which appear in diabetic patients who are apparently adequately nourished but whose diabetes has been poorly controlled for variable periods of time. These deficiencies are frequently single and their chief manifestation is peripheral neuropathy.

GROUP I

Recent trends in the dietary therapy of diabetes mellitus have been toward considerable restriction of the fat intake, in an effort to limit the tendency of diabetics toward atherosclerosis and fatty infiltration of the liver. That these ends can be accomplished on the low fat diets currently in vogue is in considerable doubt. Nonetheless, the trend continues, and with it the increased likelihood of mild clinical deficiencies of the fat-soluble vitamins.

The only vitamin in this fat-soluble group which seems to be of real clinical importance is vitamin A, which is absorbed as such from dietary sources or is synthesized in the liver or gastrointestinal mucosa from dietary carotenoid precursors. Full-blown vitamin A deficiency is manifested by nyctalopia, perifollicular hyperkeratosis and dryness of the skin, xerophthalmia, keratomalacia, and metaplasia of the mucous membranes of the upper and lower respiratory tracts and the lower urinary system. In our clinical experience, the most frequently encountered of these manifestations have been perifollicular hyperkeratoses and dry skin—especially over the arms, legs and anterior abdominal wall. It is probably of speculative interest only to question whether or not the above-mentioned metaplastic changes of cornification and desquamation in the upper respiratory tract, trachea, bronchi, renal pelves, and ureters predispose toward the infections in these areas so frequently encountered in diabetics. We have not had occasion to measure night vision in these patients, nor have we encountered the full-blown picture described above.

Theoretically, vitamin D deficiency could result under the same conditions. Actually, we are not aware of any increase in the incidence of rickets in diabetic children or of osteomalacia in diabetic adults. In theory, vitamin D deficiency might conceivably impair carbohydrate metabolism through increased

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We are grateful to the staff of the Diabetes Clinic of the Pennsylvania Hospital for their aid in observing these patients.

excretion and impaired absorption of phosphates. This could result in the reduction to less than adequate amounts of organic and inorganic phosphorus in the body fluids to form the glucose-phosphate derivatives and the enzyme-phosphate energy compounds necessary for their metabolism. So far as we are aware, no such clinico-chemical condition has been described.

Poorly controlled diabetes may produce fatty infiltration of the liver (see below) with the possibility of attendant hemorrhagic tendencies. In this instance, however, the bleeding would be due to faulty utilization of vitamin K and not due to an insufficient intake of the vitamin itself. We have seen several patients in whom there was such a tendency, not apparent clinically, but noted during the performance of prothrombin time tests as a part of liver function evaluation.

There is no clinical syndrome definitely ascribable to a deficiency of vitamin E in humans, diabetic or non-diabetic.

Of the water-soluble vitamins, those of the B group are of the most importance in our present concern. Fourteen or fifteen members of this group have been identified, but many are of no clinical significance. Deficiencies of of the more important ones are frequently encountered in diabetic patients under two sets of conditions.

First, diabetic patients are often given weight-reduction diets of 900 to 1500 calories. In patients with or without diabetes, such a diet will usually not contain the average normal daily requirement of these B vitamins. In the absence of supplementary vitamin therapy, clinical deficiency signs or symptoms may develop.

Second, there is a feeling in some circles that the carbohydrate metabolic cycle in diabetic patients may require more vitamin-containing coenzymes per gram of carbohydrate utilized or per calorie produced than are necessary in non-diabetic patients. We have nothing new to contribute to one side or the other of this thesis. If it is valid, then a patient with diabetes mellitus should develop the clinical evidences of avitaminosis B on a dietary intake that would prevent the development of similar signs in a subject without diabetes.

In either instance, the most frequently observed symptoms attributable to an absolute or relative lack of these substances have been neurasthenia, mild peripheral neuritis, anorexia, burning sensations in the mouth, soreness of the tip of the tongue, and, perhaps, mild conjunctivitis. The physical findings most often encountered have been mild conjunctival injection, a reddened tongue with smooth and serrated edges, cheilitis, mild to moderate tenderness along the major peripheral nerve trunks, and absent tendo Achilles reflexes.

We are not at all sure that these signs and symptoms can be dissociated one from another and individually attributed to a deficiency of a single member of the B group. The signs and symptoms referable to peripheral neuritis may clear with the administration of thiamine alone. However, lesions of the skin and mucous membranes have been reported as improved by the individual use of thiamine, riboflavin, niacin, and even pyridoxine (vitamin B_6) or biotin.

When a patient becomes so deficient as to develop one of the more severe and distinct syndromes, such as beriberi or pellagra, it is still true that, although the major deficiency is of a single vitamin, clinical deficiencies of other members of the B complex coexist and account for an appreciable part of the symptomatology.

It is important to recall at this point the specific roles of several members of this B group of vitamins in the metabolism of carbohydrate.[1,2,3] Thiamine, as its pyrophosphate or "cocarboxylase," is essential to an integral step in carbohydrate metabolism in which the utilization of pyruvic and related keto acids is promoted. Riboflavin is one of the components of the flavoprotein group of enzymes which serve to oxidize the reduced forms of the coenzymes in the oxidation-reduction chain responsible for carbohydrate metabolism. Niacin, similarly, is incorporated into the structure of the coenzymes, I and II, mentioned immediately above. Guest[4] and his group feel strongly that clinical and subclinical deficiencies of these vitamins may seriously interfere with carbohydrate metabolism in the

diabetic and specifically urge their introduction into the regimens for the treatment of diabetic coma. Although we have adopted this suggestion[3] we have not seen any patients with or without clinical signs of avitaminosis B in whom the omission or addition of large doses of this vitamin complex has seemed to influence the rate of recovery from ketotic coma.

Except as mentioned above, pyridoxine deficiency is of no apparent clinical importance, nor are deficiencies of biotin, pantothenic acid, or inositol.

The other water-soluble vitamins other than the B group which are of interest include vitamin C or ascorbic acid, and "vitamin P" or rutin. We have not seen clinical evidences of scurvy, mild or otherwise, among diabetics. The use of these two vitamins has been suggested for the treatment and prevention of diabetic retinopathy. The reasoning seems to be that these two substances have something to do with the integrity of the capillary wall, ascorbic acid through its contribution to the formation of intercellular ground substance, and rutin in an unascertained manner. Diabetic retinopathy consists of hemorrhages and exudates, both presumably extravasations. Therefore, the two vitamins considered may be of some help. We have had no patient in whom this therapy—or any other, for that matter—has reversed the retinopathy. There is a glimmering of an impression that their use slows the progression of the retinopathy, but we can offer no statistical support. We are currently prescribing a single tablet containing 100 mg. of ascorbic acid and 20 mg. of rutin to be taken thrice daily.

Group II

The second group of deficiencies includes two sets of manifestations.

First, many patients with diabetes mellitus of considerable duration have clinical enlargement of the liver. This is especially true of children and diabetics whose control has been intermittently poor. Histologic examination of biopsies from such livers has shown diffuse fatty infiltration of the hepatic parenchymal cells. Laboratory studies may or may not reveal evidences of mild impairment of hepatic function. Those that do have shown no characteristic pattern. The prothrombin time is occasionally abnormal, as mentioned above.

When choline is added to the patient's therapeutic regimen, the liver edge may shortly become impalpable. It is known that choline mobilizes fatty acids, donates methyl groups, and increases the phospholipid fraction in the circulating blood. All of these "lipotropic" mechanisms are apparently active in removing the fatty infiltration and thereby in reducing the size of the liver. Whether or not there is an absolute, relative, or metabolic deficiency of choline in these diabetic patients has not been determined, but the therapeutic results seem highly suggestive.

The second set of manifestations occurring in this group are neuropathic in type. For a review of this subject, the reader is referred to two recent papers[5,6] and their bibliographies.

It is important to remember that the signs and symptoms of peripheral neuritis in a diabetic patient may be due to thiamine deficiency and will respond to treatment with adequate amounts of that vitamin. There is also a somewhat vague entity known as "ischemic neuropathy." The manifestations are those of peripheral neuritis, but nerve-trunk tenderness is usually absent. The symptoms in these cases are supposed to be due to neural damage from deficient blood supply through arteriolar sclerosis of the vasa nervorum. If the local circulation is capable of responding to various therapeutic vasodilatation measures and if the neuritic symptoms are improved concomitantly, then, in retrospect, one diagnoses "ischemic neuropathy."

Finally, one is left with the true diabetic neuropathies. The manifestations include nocturnal muscular cramps, paresthesias, hypesthesia, and hypalgesia, loss of vibration and position sense in the lower extremities, muscular weakness and atrophy, trophic ulcers, optic neuritis, Argyll pupils, Charcot joints, and autonomic imbalances affecting the bladder, superficial circulation, and sweating and pilomotor responses.

No one as yet knows why diabetics develop such neuropathy. Evidence is accumulating that it is a manifestation of a nutritional deficiency. The similarity to the combined system disease of pernicious anemia is obvious. When it is noted that many of these diabetic patients also have a sprue-like steatorrhea without creatorrhea, smooth red tongue, gastric anacidity, and increased spinal fluid protein, the similarity increases. Many of these diabetic patients also have an anemia, but it is more frequently normocytic than macrocytic.

Following the identification of vitamin B_{12} as the active liver principle lacking in pernicious anemia, and the introduction of suggestive evidence that it is the extrinsic factor of Castle as well, its effect on the neurologic abnormalities was followed with interest. Folic acid, an earlier entrant, had failed to affect these satellite symptoms. Vitamin B_{12} proceeded to produce prompt and lasting neurological remissions in pernicious anemia.

On an empirical basis, founded insecurely on the noted similarity between the two syndromes, diabetic neuropathy was then treated with Vitamin B_{12}. Contrary to the experience of others,[6] many of our patients with mild to moderate neuropathic symptoms experienced prompt and lasting relief from symptoms on 30 μg. of vitamin B_{12} daily for 3 to 5 days. Several patients experienced recurrent exacerbations of their symptoms and are apparently in the position of requiring a maintenance dose. One patient with ataxia, nocturnal diarrhea, peripheral neuritic symptoms, and a left sixth cranial nerve palsy had complete clearing of all these manifestations within a month of therapy with Vitamin B_{12}. On the other hand, several other patients with severe neuropathies have apparently reached an irreversible stage and have been helped only slightly or not at all by much larger doses over longer periods of time.

Sancetta, Ayers, and Scott[7] successfully treated twelve diabetics with neurologic disturbances by giving 15 to 30 μg. of vitamin B_{12} daily for a week or two, and then maintaining a similar dose once or twice a week.

The exact mechanism of the production of this peculiar and unique type of vitamin deficiency in diabetic patients remains undiscovered. The biochemical and patho-physiological processes involved have not been elucidated. The relationship between vitamin B_{12} and pregnant mammalian liver extract[8,9] is undetermined. Most important, the factors determining the success or failure of therapy with these two substances are a mystery.

Conclusions

Clinical vitamin deficiencies in patients with diabetes mellitus occur (a) when patients are given low calorie and/or low fat diets without supplementary vitamin therapy, (b) in otherwise well-nourished patients whose diabetes has been poorly controlled for variable periods of time.

In the first group, the perifollicular hyperkeratosis and dry skin of avitaminosis A and the peripheral neuritis and mucous membrane changes of avitaminosis B are most frequently encountered.

In the second group, hepatic enlargement responding to choline therapy and diabetic neuropathy responding to treatment with vitamin B_{12} are discussed.

Theoretical considerations regarding other deficiencies are recounted.

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Resumen

Hipovitaminosis clínicas en pacientes con diabetes mellitus

Aparecen las hipovitaminosis clínicas en pacientes con diabetes *mellitus:* (a) cuando se suministra a los pacientes una dieta pobre en calorías o en grasas o bien en las dos, sin vitaminoterapía suplementaria; (b) en pacientes de otro modo bien nutridos cuya diabetes ha sido mal controlada durante períodos de tiempo variables.

En el primer grupo, se encuentran con mayor frecuencia la hiperqueratosis perifolicular y el xeroderma característicos de la avitaminosis A, y la neuritis periférica y las alteraciones de la membrana mucosa asociadas a la avitaminosis B.

Del segundo grupo se discuten la hepatomegalia—que responde a la terapéutica con colina, y la neuropatia diabética—obedeciendo a la vitaminoterapía B_{12}.

Se presentan consideraciones teóricas sobre otras deficiencias.

CALORIC VALUES FOR COMMON "SNACK" FOODS

CANDIES	Amount or Average Serving	Calorie Count
Chocolate Bars, 5¢ size		
Plain	1 bar (1¼ oz.)	190
With nuts	1 bar	275
Chocolate Covered Bar	1 bar	250
Chocolate Cream, Bon Bon, Fudge	1 piece 1" square	90
Caramels		
Plain	1 piece ¾" cube	35
Chocolate nut caramels	1 piece	60
DESSERTS		
Pie		
Fruit—Apple, etc.	1/6 pie 1 Average Serving	560
Custard	1/6 pie 1 Average Serving	360
Lemon Meringue	1/6 pie 1 Average Serving	470
Pumpkin pie with whipped cream	1/6 pie 1 Average Serving	460
Cake		
Iced layer—2 layers white cake	1 Average Serving	345
Fruit—thin slice ¼"	1 Average Serving	125
SWEETS		
Ice Cream		
Plain vanilla	1/6 qt. serving	200
Chocolate and other flavors	1/6 qt., ⅔ cup	230
Milk sherbet	1/6 qt., ⅔ cup	250
Sundaes small chocolate nut with whipped cream	Average	400
Ice cream sodas, chocolate	10 oz. glass	270
MIDNIGHT SNACKS for ICE-BOX RAIDERS		
Cold potato	½ medium	65
Chicken leg	1 average	88
Glass milk	7 oz. glass	140
Mouthful of roast	½" × 2" × 3"	130
Piece of cheese	¼" × 2" × 3"	120
Left-over beans	½ cup	105
Brownie	¾" × 1¾" × 2¼"	300
Cream-puff	4" diameter	450

(Courtesy of Smith, Kline & French Laboratories, Philadelphia)

Effects of B VITAMIN DEFICIENCIES *on the Leukocyte Response to* EPINEPHRINE AND CORTICOTROPIN (ACTH)

By B. H. ERSHOFF, PH.D.* AND F. D. PARROTT, JR., B.S.†

IT IS WELL established that the pituitary-adrenal system is activated under conditions of stress and that the hypophysectomized or adrenalectomized animal has an impaired ability to withstand stressor agents. Resistance to stressor agents may also be impaired as a result of nutritional deficiency.[1,2] There is evidence to indicate that at least in the case of some nutrients the impaired resistance to stressor agents during malnutriture is due not primarily to the deficiency *per se* but rather to an impaired production of pituitary and adrenal hormones which are required in increased amounts during conditions of stress. Thus Reade and Morgan[3] found that adrenal cortical extract as well as riboflavin restored the impaired gluconeogenesis of riboflavin-deficient rats to normal under conditions of anoxic anoxia;[3,4] while adrenal cortical extracts corrected the reduced diuretic response to ingested water and the lowered resistance to water intoxication of riboflavin-deficient[5] and pyridoxine-deficient[6] rats. In the present communication, data are presented concerning the leukocyte response of rats deficient in B vitamins following the administration of epinephrine and corticotropin (ACTH).

Recent findings indicate that activation of the pituitary-adrenal system results, in the normal animal, in a reduction of the peripheral blood lymphocyte and eosinophile count. This reduction is apparently due to an increased production of adrenal corticosteroids, inasmuch as corticosterone and corticotropin administration both duplicate this effect.[7-10] Corticosterone, however, exerts this effect in the adrenalectomized animal while corticotropin does not. Administration of epinephrine or exposure to any one of a number of nonspecific stressor agents also results in lymphopenia and eosinopenia, presumably due at least in part to corticotropin discharge.[11,12] It would appear, therefore, that the leukocyte response to stressor agents might be employed within limits as an indicator of pituitary-adrenal function. Furthermore, variations in the leukocyte response after epinephrine, corticotropin, and cortisone administration might indicate whether pituitary-adrenal function was impaired at the pituitary, adrenal, or peripheral tissue level. Such a test based on alterations in the eosinophile count has been proposed.[9] In the present experiment, however, rats deficient in various vitamins showed virtually a complete absence of eosinophiles in their peripheral blood; hence pituitary-adrenal function could not be tested by alterations in the eosinophile count. Changes in the lymphocyte count in response to epinephrine, corticotropin, or cortisone administration, however, appeared to offer promise as a test for pituitary-adrenal function. If lymphopenia failed to occur following the injection of

From the Emory W. Thurston Laboratories, Los Angeles, California.

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epinephrine to a nutritionally-deficient rat but did result after corticotropin administration, it might indicate as suggested by Recant *et al.*[9] impaired response at the pituitary level (inadequate corticotropin secretion). If lymphopenia occurred after cortisone administration but not after the injection of corticotropin, it might indicate failure of response at the adrenal level (impaired formation of cortical hormones). The absence of lympophenia after cortisone administration might indicate failure of response at the peripheral tissue level.

Procedure

Experiment 1. Effects of Corticotropin Administration on the Leukocyte Response of Rats Deficient in Thiamine, Riboflavin, and Pantothenic Acid

The basal ration employed in the present experiment consisted of sucrose, 60 per cent; casein*, 25 per cent; salt mixture**, 5 per cent; and cottonseed oil (Wesson), 10 per cent. To each kg. of the above diet were added the following synthetic vitamins: thiamine hydrochloride, 40 mg.; riboflavin, 40 mg.; pyridoxine hydrochloride, 40 mg.; calcium pantothenate, 80 mg.; nicotinic acid, 60 mg.; ascorbic acid, 200 mg.; biotin, 5 mg.; folic acid, 10 mg.; *p*-aminobenzoic acid, 400 mg.; inositol, 800 mg.; vitamin B_{12}, 150 μg.; 2-methyl-napthoquinone, 10 mg.; and choline chloride, 2 Gm. Each rat also received 3 times weekly a vitamin A-D concentrate† containing 50 U. S. P. units of vitamin A and 5 U.S.P. units of vitamin D, and once weekly 4.5 mg. of alpha-tocopherol acetate In addition to the basal ration, the following diets were also employed: (a) basal ration with thiamine hydrochloride omitted, (b) basal ration with riboflavin omitted, and (c) basal ration with calcium pantothenate omitted.

Fifty female rats of the Long-Evans strain were selected for the present experiment at 25 to 28 days of age and an average weight of 56.3 Gm. Animals were kept in individual metal cages with raised screen bottoms to present access to feces and were fed the above diets *ad libitum* (10 rats per group). Food consumption was determined daily for each rat. In addition to the 4 groups indicated above, a fifth group was also employed, consisting of 10 rats pair-fed the basal ration in amounts equal to that ingested daily by rats on the thiamine-free ration. Animals on the thiamine, riboflavin, and pantothenic acid-deficient diets attained maximum weight between the 14th and 18th day of feeding and thereafter gradually lost weight. Rats in the pair-fed series attained maximum weight on the 24th day of feeding. Those fed the basal ration *ad libitum* continued to gain weight throughout the experimental period.

During the fourth week of feeding, surviving animals in each group received a single intraperitoneal injection of 4 mg. ACTH‡ per 100 Gm. body weight. Immediately before the injection and at 2, 4, and 7 hours afterward specimens were taken of tail blood of all rats and total and differential white cell counts determined. Differential counts were made on smears stained with Wright's stain, 100 cells on each of 2 sides being employed for each analysis. Results are summarized in Table I.

Results

The blood lymphocyte count was significantly reduced in all rats 2 hours after corticotropin administration. On a percentage basis, reductions varied from 39 to 47 per cent. Differences between the various groups were not statistically significant. The findings indicate, therefore, that under conditions of the present experiment thiamine, riboflavin, and pantothenic acid deficiency did not impair the ability of the adrenal gland to produce lymphopenia-producing cortical hormones in response to corticotropin stimulation nor of the peripheral tissues to respond thereto. Differences were observed, however, between the various groups in the lymphocyte response subsequent to the second hour post injection. In the basal ration-*ad libitum* series the total lymphocyte count was restored to substantially pre-injection levels 4 hours after injection. In the thiamine-free and basal ration-pair-fed series, the lymphocyte count was approaching but was still below pre-injection levels 7 hours after injection. In the riboflavin-free series, the lymphocyte count was lower 7 hours after injection than in any of the previous counts. Rats in the pantothenic acid-free series exhibited an initial drop in blood lymphocytes 2 hours after corticotropin injection, a return to pre-injection levels by 4 hours but a subsequent drop by the seventh hour.

A significant difference was observed be-

* Vitamin Test Casein, General Biochemicals, Inc., Chagrin Falls, Ohio.

** Hubbel, Mendel and Wakeman Salt Mixture, General Biochemicals, Inc., Chagrin Falls, Ohio.

† Nopco Fish Oil Concentrate, assaying 800,000 U.S.P. units of vitamin A and 80,000 U.S.P. units of vitamin D per Gm.

‡ Acthar®, Armour & Co., Chicago, Illinois.

TABLE I

Effect of Thiamine, Riboflavin, and Pantothenic Acid Deficiency on the Leukocyte Response of Rats Administered ACTH (Corticotropin)

Dietary Group	Number of Animals*	Body Weight at Time of Injection (Gm.)	Average Food Consumption per Rat for First 24 Days of Feeding (Gm./Day)	Leukocyte Counts				Change in Lymphocyte Count 2 Hours after Injection† (Per Cent)	Change in Granulocyte Count 4 Hours after Injection (Per Cent)
				Pre-injection	Post-injection 2 hours	Post-injection 4 hours	Post-injection 7 hours		
Basal ration (*ad libitum*)	10	153	12.4					−39 ± 4.6	+164
Total WBC				14,670	12,930	18,490	15,510		
Lymphocytes				11,589	7,112	10,354	9,306		
Total granulocytes				3,081	5,818	8,136	6,204		
% granulocytes				21	45	44	40		
Basal ration (pair-fed)	10	111	9.9					−47 ± 4.2	+197
Total WBC				11,575	10,908	14,115	10,908		
Lymphocytes				8,913	4,690	6,211	5,672		
Total granulocytes				2,662	6,218	7,904	5,236		
% granulocytes				23	57	56	48		
Thiamine-free	7	82	9.9					−40 ± 7.3	+124
Total WBC				6,300	6,314	7,893	8,314		
Lymphocytes				3,906	2,336	2,526	3,408		
Total granulocytes				2,394	3,978	5,367	4,906		
% granulocytes				38	63	68	59		
Riboflavin-free	10	66	8.4					−41 ± 5.8	−8
Total WBC				11,444	8,031	8,566	7,044		
Lymphocytes				7,439	4,417	4,883	3,733		
Total granulocytes				4,005	3,614	3,683	3,311		
% granulocytes				35	45	43	47		
Pantothenic acid-free	8	79	9.0					−43 ± 5.9	+180
Total WBC				8,980	7,213	12,160	7,210		
Lymphocytes				6,933	3,946	6,445	4,470		
Total granulocytes				2,047	3,267	5,715	2,740		
% granulocytes				23	45	47	38		

Data for total WBC, lymphocytes and total granulocytes are expressed in cells per cubic millimeter.

* Initially 10 rats were in each group. The number of animals listed in the table indicates the number of animals alive when the last blood specimen was taken and on which data are based.

† Including standard error of the mean calculated as follows: $\sqrt{\frac{\overline{d^2}}{n}} / \sqrt{n}$ where "d" is the deviation from the mean and "n" is the number of observations.

tween riboflavin-deficient rats and those on other rations in respect to the granulocyte response. In all groups tested, with the exception of the riboflavin-free series, a significant increase occurred 4 hours post injection in the number of peripheral polymorphonuclear leukocytes per cu. mm. of blood (average increase 166 per cent over pre-injection levels, range 124 to 197 per cent); in the riboflavin-deficient series, however, the polymorphonuclear leukocyte count 4 hours post injection was decreased (8 per cent).

Procedure

Experiment 2. Effects of Epinephrine Administration on the Leukocyte Response of Rats Deficient in Thiamine, Riboflavin, and Pantothenic Acid

Sixty male rats of the University of Southern California strain were selected at 21 to 23 days of age and an average weight of 44.2 Gm. for the present experiment. The diets fed and the experimental procedure employed were similar to those described in Experiment 1 (12 animals per group). Food consumption was not determined, however, except for rats in the

thiamine-free and basal ration pair-fed series. During the fourth week of feeding, surviving animals in each group received a single intraperitoneal injection of 0.03 mg. adrenalin* per 100 Gm. body weight. Immediately before the injection, and at 3 and 24 hours afterward, specimens were taken of the tail blood of all rats; and total and differential white cell counts and direct eosinophile counts determined. Similar tests were also conducted with 36 female rats of the USC strain fed the riboflavin-free, pantothenic acid-free and basal ration (*ad libitum*) diets (12 animals per group) and with 12 female rats depleted of vitamin A (see reference 13 for procedure and diet employed). Results are summarized in Table II.

Results

A significant reduction in the peripheral blood lymphocyte count was observed 3 hours after epinephrine administration in all rats fed the basal ration or diets deficient in thiamine or riboflavin. In contrast, both male and female rats deficient in pantothenic acid developed a significant lymphocytosis 3 hours after epinephrine administration. The reduction in lymphocytes of rats deficient in thiamine and riboflavin was less marked than that of animals fed the basal ration *ad libitum* but did not differ significantly from that of rats in the basal ration-pair-fed series. It would appear, therefore, that caloric restriction *per se* and not the concomitant thiamine or riboflavin deficiency was responsible, at least in part, for the decreased lymphocyte response observed in these rats.

A significant reduction in eosinophiles occurred 3 hours after epinephrine administration in male rats fed the riboflavin-deficient or basal ration (either *ad libitum* or pair-fed) and in female rats on the basal ration. In all other series, however, both in male and female rats, eosinophiles were virtually absent from the pre-injection count; hence further reduction of this blood constituent appeared to have little value as an indicator of adrenocortical function.

In contrast to the reduction in polymorphonuclear leukocytes observed in riboflavin-deficient rats injected with corticotropin, the administration of epinephrine resulted both in male and female riboflavin-deficient rats in a significant polymorphonuclear leukocytosis which did not differ significantly from that observed in similarly treated animals on the basal ration. Twenty-four hours after injection, blood leukocytes had returned in virtually all cases to substantially pre-injection levels. No impairment in the lymphocyte or polymorphonuclear leukocyte response was noted in female rats depleted of vitamin A.

* Adrenalin Chloride® Solution 1: 1000 adrenalin, brand of epinephrine, Parke Davis & Co., Detroit.

Procedure

Experiment 3. Comparative Effects of (1) a Single and (2) Multiple Injections of Epinephrine on the Leukocyte Response of Pyridoxine-deficient Rats.

Two groups of male rats of the University of Southern California strain were employed in the present experiment. One group consisted of 12 animals which were in the basal ration-*ad libitum* series in Experiment 2. The other group consisted of 12 rats which had been placed at weaning (21 to 23 days of age) on a purified ration identical to the basal ration but from which pyridoxine hydrochloride had been omitted. Animals were fed *ad libitum* in both groups. During the fourth week of feeding, each rat received a single intraperitoneal injection of 0.03 mg. adrenalin® per 100 Gm. body weight, and the leukocyte count was determined immediately before and at 3 and 24 hours post injection. The epinephrine injections were repeated daily until a total of 10 injections had been administered to each rat. Immediately before and at 3 and 24 hours after the last injection, specimens were taken of the tail blood of all rats, and total and differential white cell counts and direct eosinophile counts were determined. Results are summarized in Table III.

Results

A significant reduction in the peripheral blood lymphocyte count was observed both in pyridoxine-deficient rats and those on a complete diet 3 hours after the administration of the first injection of epinephrine. After 10 daily injections, however, the lymphopenic response was absent in pyridoxine-deficient rats, although relatively unimpaired in supplemented controls. After 10 daily injections, further, the relative increase in polymorphonuclear cells was significantly less for pyridoxine-deficient rats than for those on the complete ration.

Food consumption data were not determined in the present experiment and pair-fed controls

TABLE II

Effects of Thiamine, Riboflavin, and Pantothenic Acid Deficiency on the Leukocyte Response of Rats Administered Epinephrine

Dietary Group	Number of Animals*	Body Weight at Time of Injection (Gm.)	Leukocyte Counts			Change in Lymphocyte Count 3 Hours after Injection† (Per Cent)	Change in Granulocyte Count 3 hours after Injection (Per Cent)
			Pre-injection	Post-injection			
				3 hours	24 hours		
Males							
Basal ration (*ad libitum*)	12	143				−47 ± 2.9	+181
Total WBC			15,666	15,221	13,038		
Lymphocytes			12,634	6,700	10,655		
Total granulocytes			3,032	8,521	2,383		
% granulocytes			19	55	18		
Eosinophiles			341	71	258		
Basal ration (pair-fed)	12	107				−33 ± 5.3	+539
Total WBC			11,550	17,829	13,578		
Lymphocytes			9,787	6,570	10,391		
Total granulocytes			1,763	11,259	3,187		
% granulocytes			15	63	23		
Eosinophiles			283	104	166		
Thiamine-free	11	83				−26 ± 5.8	+324
Total WBC			10,255	15,650	10,095		
Lymphocytes			7,958	5,919	7,690		
Total granulocytes			2,297	9,731	2,405		
% granulocytes			22	60	23		
Eosinophiles			63	15	15		
Riboflavin-free	10	60				−19 ± 9.2	+335
Total WBC			9,221	15,293	9,893		
Lymphocytes			7,026	5,735	7,380		
Total granulocytes			2,195	9,558	2,513		
% granulocytes			24	63	25		
Eosinophiles			228	93	143		
Pantothenic acid-free	9	78				+39 ± 22.4	+401
Total WBC			2,880	5,432	2,588		
Lymphocytes			2,485	3,455	2,127		
Total granulocytes			395	1,977	461		
% granulocytes			14	36	18		
Eosinophiles			8	0	0		
Females							
Basal ration (*ad libitum*)	12	126				−16 ± 3.9	+211
Total WBC			12,583	17,986	13,425		
Lymphocytes			9,337	7,876	10,340		
Total granulocytes			3,246	10,110	3,085		
% granulocytes			26	56	23		
Eosinophiles			186	100	212		
Riboflavin-free	11	61				− 6 ± 6.7	+354
Total WBC			9,570	17,170	10,700		
Lymphocytes			7,312	6,900	7,683		
Total granulocytes			2,258	10,270	3,017		
% granulocytes			24	60	28		
Eosinophiles			9	10	33		

Pantothenic acid-free	9	66				+35 ± 17.4	+544
Total WBC			6,025	14,819	14,800		
Lymphocytes			4,712	6,368	9,266		
Total granulocytes			1,313	8,451	5,534		
% granulocytes			22	57	37		
Eosinophiles			29	38	17		
Vitamin A-free	12	111				−15 ± 7.3	+342
Total WBC			7,830	12,830	8,780		
Lymphocytes			6,093	5,149	6,991		
Total granulocytes			1,737	7,681	1,789		
% granulocytes			22	61	21		
Eosinophiles			8	0	0		

Data for total WBC, lymphocytes, eosinophiles and total granulocytes are expressed in cells per cubic millimeter.

* See footnote *, Table I.

† See footnote †, Table I.

TABLE III

Comparative Effects of (1) a Single and (2) Multiple Doses of Epinephrine on the Leukocyte Response of Pyridoxine-deficient Rats

Group	Body Weight (Gm.)	Number of Animals*	Leukocyte Count			Change in Lymphocyte Count 3 hours post Injection† (Per Cent)	Change in Granulocyte Count 3 hours post Injection (Per Cent)
			Pre-injection	Post-injection 3 hours	Post-injection 24 hours		
Pyridoxine-deficient Series							
1st injection	100.6	10				−41 ± 8.1	+164
Total WBC			9,883	11,589	8,250		
Lymphocytes			7,086	4,185	5,560		
Total granulocytes			2,797	7,404	2,690		
% granulocytes			28	64	33		
Eosinophiles			156	83	111		
10th injection	92.1	8				− 2 ± 7.6	+ 80
Total WBC			10,980	14,231	13,430		
Lymphocytes			6,694	6,533	7,360		
Total granulocytes			4,286	7,698	6,070		
% granulocytes			39	54	45		
Eosinophiles			50	0	8		
Basal Ration (*ad libitum*) Series							
1st injection	143	12				−47 ± 2.9	+181
Total WBC			15,666	15,221	13,038		
Lymphocytes			12,634	6,700	10,655		
Total granulocytes			3,032	8,521	2,383		
% granulocytes			19	55	18		
Eosinophiles			341	71	258		
10th injection	155	12				−34 ± 8.5	+247
Total WBC			15,583	21,750	17,250		
Lymphocytes			11,516	7,624	11,161		
Total granulocytes			4,067	14,126	6,089		
% granulocytes			26	65	35		
Eosinophiles			100	0	133		

Data for total WBC, lymphocytes, eosinophiles and total granulocytes are expressed in cells per cubic millimeter.

* See footnote *, Table I.

† See footnote †, Table I.

were not employed. The possibility, therefore, that caloric restriction and not pyridoxine deficiency *per se* was responsible for the observed results has not been eliminated.

Discussion

It is well established that epinephrine administration stimulates pituitary-adrenal function and elicits corticotropin discharge from the anterior pituitary gland. It has been reported that epinephrine activates the adrenal cortex only when the pituitary gland is intact;[9,14-16] and that the adrenocorticotropic properties of epinephrine are due solely to the release of corticotropin. There is evidence, however, that massive doses of epinephrine may stimulate cortical hormone production even in the absence of the pituitary. Thus Hungerford[17] observed that the number of circulating blood lymphocytes was lowered after administering a large dose of epinephrine to both normal and hypophysectomized but not in adrenalectomized rats. Similarly large doses of epinephrine and corticotropin were both effective in causing a significant reduction in the number of thoracic duct lymphocytes in normal and hypophysectomized but not in adrenalectomized rats.[18] With smaller doses of epinephrine, however, it is the consensus of opinion that the cortical stimulation is due primarily if not entirely to the corticotropin discharge. Changes in the peripheral lymphocyte count in response to epinephrine administration would appear, therefore, to result from the liberation of pituitary adrenocorticotropic hormone and the consequent increase in adrenal cortical hormone secretion.

Results of the present experiment indicate that rats deficient in thiamine, riboflavin, pyridoxine, and vitamin A responded to a single injection of epinephrine with a significant reduction in the peripheral blood lymphocyte count 3 hours after injection. These findings indicate that under conditions of the present experiment a deficiency of the above vitamins did not impair the ability (1) of the adrenal glands to produce lymphopenia-producing cortical hormones in response to cortical stimulation, (2) of the peripheral tissues to respond to such hormones, and (3) of epinephrine to evoke the discharge of pituitary corticotropin. Rats deficient in pantothenic acid, however, showed no reduction in the peripheral blood lymphocyte count after epinephrine administration, but, on the contrary, a significant lymphocytosis. When corticotropin was administered, however, the lymphopenic response of pantothenic acid-deficient rats did not differ significantly from that of rats on a complete ration.* It would appear from these findings that the failure of pantothenic acid-deficient rats to exhibit lymphopenia after epinephrine administration was due to an inadequate adrenocorticotropic hormone secretion. Available data do not indicate, however, whether the impaired corticotropin secretion was the result of (1) failure of epinephrine to stimulate the anterior pituitary of pantothenic acid-deficient rats, (2) inadequate corticotropin synthesis, either in amount or kind, or (3) failure of the secretory mechanism.

The failure of epinephrine to produce lymphopenia in pantothenic acid-deficient rats is in accord with the findings of Dumm *et al.*[19] that the reduction in blood lymphocytes of rats subjected to the stress of swimming for 25 minutes in water at 25° C. was partially abolished in animals fed a pantothenate-deficient diet. Dumm *et al.*,[19] however, in contrast to present findings, observed that the lymphopenic response was also impaired in pantothenate-deficient rats administered corticotropin, although less so than in the swimming stress.

The reduction in peripheral blood lymphocytes following a single injection of epinephrine is considered an index of adrenocortical activation in response to the discharge of preformed corticotropin from the anterior pituitary. As such, it is essentially a response of the organism to acute stress. It is possible, however, as Samuels[20] has pointed out, that a nutritionally-deficient animal may have sufficient corticotropin in its pituitary to meet

*In the present experiment the effects of epinephrine and corticotropin administration were determined on rats of different strains; hence strain differences may have contributed to the diverse results. In subsequent work, however, similar findings were obtained following epinephrine and corticotropin administration to rats of the same (Long-Evans) strain.

body requirements for this factor during an acute stress reaction, but that such animals may have an impaired ability to synthesize corticotropin and other hormones in the amounts required during repeated or chronic stress. The findings in Experiment 3 (pyridoxine-deficient rats receiving multiple doses of epinephrine) support this hypothesis. Thus it was observed that pyridoxine-deficient rats did not differ from animals on a complete ration in their lymphopenic response to a single injection of epinephrine; but after 10 daily injections the lymphopenic response was absent in pyridoxine-deficient rats, although relatively unimpaired in supplemented controls. Available data do not indicate whether this failure of a lymphopenic response was due to a failure at the pituitary (impaired ACTH secretion), adrenal (impaired response to adrenocortical stimulation), or peripheral tissue (impaired response to lymphopenic corticoids) level. In view of pyridoxine's role in protein metabolism, one might suspect impairment at the pituitary level as a distinct possibility.

Leukocytes and Hormones

The significance of polymorphonuclear leukocytosis in animals subjected to stress requires clarification. A number of non-specific stressor agents cause a significant increase in the polymorphonuclear cell count.[11,12] It is questionable, however, to what extent activation of the pituitary-adrenal system is responsible for this effect. Both epinephrine and corticotropin administration cause polymorphonuclear leukocytosis in the normal animal. Neither hypophysectomy nor adrenalectomy, however, counteracts the effectiveness of epineprine in this regard.[17] Similarly, adrenalectomy does not prevent the increase in polymorphonuclear cells following the administration of corticotropin.[10] Furthermore, cortisone has an effect opposite to that of corticotropin.[10] It has been suggested by Palmer *et al.*[10] that the increase in polymorphonuclear cells following injection of corticotropin may be an extra-adrenal effect of either ACTH or some other substance present in the pituitary preparations employed.

It would appear from the above findings that alterations in the polymorphonuclear cell count in response to stressor agents have little value as an indicator of pituitary-adrenal function, at least in the rat. No explanation can be offered at the present time as to the possible cause or significance of the observation that riboflavin-deficient rats fail to exhibit an increase in polymorphonuclear cells following corticotropin administration. It is of interest, however, that riboflavin deficiency did not impair the increase in polymorphonuclear cells following the administration of epinephrine.

The present investigation of pituitary-adrenal function in nutritionally-deficient rats employed the reduction in peripheral lymphocyte count as an index of adrenocortical activation. It is well established, however, that the various indices of pituitary-adrenal function may yield conflicting results to any given stressor agent. There is evidence that a number of corticoids are present in the adrenal gland, and these may vary both in amount and kind in the cortical secretions produced in response to different stressor agents. Evidence of adrenal activation obtained with one index, therefore, does not rule out the possibility of an impaired production of corticoids which may be involved in other indices. There is also evidence that more than one adrenocorticotropic hormone may be produced. Thus as far back as 1942 Golla and Reiss[21] reported the presence of two corticotropic factors in the pituitary—one affecting adrenal weight, the other the distribution of lipoid in the adrenal cortex. More recently it was noted that certain pituitary extracts are especially active in reducing the ascorbic acid content of the adrenals of hypophysectomized rats, while other mainly cause an increase in adrenal weight under similar conditions.[22] Talbot *et al.*[23] have recently postulated the presence of two corticotropic hormones in man, one concerned with 11-17-oxycorticosteroid, the other with 17-ketosteroid formation. It is possible, therefore, that nutritional deficiencies may condition not only the response of the adrenal cortex and the target organs of its secretions, but also the production and secretion of corticotropic hormones

(or other substances released simultaneously from the pituitary with corticotropin as a result of a given stressing situation that may modify the action of corticotropin). Further studies are indicated concerning the effects of nutritional deficiencies on other indices of pituitary-adrenal function than the reduction in the peripheral lymphocyte count.

Summary

Determinations were made of the lymphocyte response to epinephrine administration of rats fed a complete diet and of animals deficient in thiamine, riboflavin, pyridoxine, pantothenic acid, and vitamin A. A significant reduction in the peripheral lymphocyte count (presumably indicative of activated pituitary-adrenal function) occurred in all rats 3 hours post injection, with the exception of those depleted of pantothenic acid. In the latter group, in place of the usual lymphopenic response, a significant lymphocytosis occurred. Rats deficient in pantothenic acid, however, showed a significant lymphopenia following the administration of corticotropin (ACTH). It was concluded, therefore, that the adrenals of pantothenic acid-deficient rats could respond to cortical stimulation but that the pituitaries of such animals failed to liberate sufficient corticotropin in response to epinephrine administration to stimulate the production of lymphopenia-producing corticoids.

Determinations were made of the lymphocyte response of pyridoxine-deficient rats after (1) a single and (2) repeated injections of epinephrine. No significant difference in lymphopenic response was observed between pyridoxine-deficient rats and those on a complete ration after a single injection of epinephrine; after 10 daily injections, however, the lymphopenic response was absent in pyridoxine-deficient rats although relatively unimpaired in supplemented controls.

The above findings are discussed in respect to pituitary-adrenal function.

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Resumen

Efectos de las deficiencias de vitamina B sobre la respuesta de los leucocitos a la administración de epinefrina y ACTH en la rata

Se hicieron determinaciones de la respuesta de los linfocitos a la administración de epinefrina en ratas alimentadas con una dieta completa y en animales deficientes en tiamina, riboflavina, piridoxina, ácido pantoténico y vitamina A. Se obtuvo una disminución importante en el recuento de linfocitos periféricos (indicativa de la activización de la función pituitarioadrenal) a las 3 horas de inyectadas las ratas, excepto en aquellas deficientes en ácido pantoténico. En este grupo, en lugar de la respuesta linfopénica acostumbrada, se produjo una linfocitosis notable. Las ratas deficientes en ácido pantoténico, sin embargo, mostraron una linfopenia notable después de la administración de la hormona adrenocorticótropa (ACTH). Se concluyó, por eso, que las glándulas adrenales de las ratas deficientes en ácido pantoténico pudieron responder a la estimulación cortical, pero que las hipófisis de las mismas no consiguieron liberar una cantidad suficiente de ACTH en respuesta a la administración de epinefrina para estimular la producción de corticoïdes productores de linfopenia.

Se hicieron también determinaciones de la respuesta de los linfocitos en ratas deficientes en piridoxina después de (1) una sola inyección y (b) inyecciones repetidas de epinefrina. En lo que concierne a la respuesta linfopénica a la administración de una sola inyección de epinefrina, no se observó ninguna diferencia entre las ratas deficientes en piridoxina y las alimentadas con una dieta completa; pero después de 10 inyecciones diarias, la respuesta linfopénica estaba ausente en las ratas deficientes en piridoxina, mientras que en los animales de control, estaba relativamente intacta.

Se discuten los datos referidos con respecto a la función pituitarioadrenal.

A slender and restricted diet is always dangerous in chronic diseases, and also in acute diseases, where it is not requisite. And again, a diet brought to the extreme point of attenuation is dangerous; and repletion, when in the extreme, is also dangerous.

—Hippocrates (*Aphorisms*, Section I, Number 4)

Persons who are naturally very fat are apt to die earlier than those who are slender.

—Hippocrates (*Aphorisms*, Section II, Number 44)

The Use of FORMULA DIETS *Administered via Polyethylene Tube or Orally for* CONSTANT INTAKE (BALANCE) STUDIES

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IN RECENT YEARS the value of the balance type of study in clinical investigation has become increasingly apparent. Unfortunately, because of the difficulties inherent in preparation of constant diets, the use of this investigative tool has been confined to relatively few institutions. Further, even under the best conditions the use of rotating diets as described by Reifenstein *et al.*[1] makes for less than absolute constancy of intake, and hence requires very prolonged studies if dependence is to be placed upon the results which are obtained.

In this laboratory during the past year, increasing use has been made of formula diets, the material in most instances being administered at hourly intervals through a polyethylene tube (inside diameter 0.047 mm.), the tip of which lies in the stomach or in the duodenum (the latter in the case of diets containing very large amounts of fat).[2] Initially, this dietary program was used to permit the administration of a very high fat intake. In the course of this work, it became apparent that formula feeding had much to recommend it in terms of simplicity, and particularly in terms of absolute constancy of food intake. In the pages which follow, prototypes of a number of formula diets will be described from the standpoint of composition and preparation.

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COMPOSITION AND PREPARATION

Formulae for Tube Feeding

Diet 1 (Table I)

Method of Preparation

In the preparation of this and subsequent diets, all constituents are weighed accurately on a torsion balance. The potassium chloride solution (previously prepared as a 20 per cent solution) is measured by pipette. The water is measured in a graduated cylinder. After initial washing, all utensils are *thoroughly* rinsed with distilled water. A portion of water is heated to dissolve the sucrose. The protein hydrolysate is added to 400 cc. of water and the mixture is made homogenous by using a blender. The powdered whole milk is blended in a similar fashion, reblending after thorough removal of the residue which adheres to the side of the bowl. The blends are then mixed manually with the potassium chloride in a suitable container, using the remaining portion of water to rinse the containers. The material is chilled in ice water and refrigerated. One hundred cc. of this mixture is administered through the tube every hour, using a chemically clean "luer-lok" syringe with a No. 18 needle. All formulae must be stirred well each time before measuring and administering.

TABLE I

Diet 1—Milk, Protein Hydrolysate,* Sugar Formula†

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Powdered whole milk	100 Gm.	25.8 Gm.	26.7 Gm.	38.0 Gm.	1296 mgm.	390 mgm.
Protein hydrolysate*	100 Gm.	75	—	—	200	1800
Sucrose	230 Gm.	—	—	230	—	—
Potassium chloride	2 Gm.	—	—	—	1044	—
Distilled water	2150 cc.					
Total volume:	2400 cc.	100.8	26.7	268	2540	2190
Total calories:	1719					

* Protolysate®.

† Composition obtained from Chatfield and Adams,[8] in instances where analyses not carried out in this laboratory.

TABLE II

Diet 2—Casec®, Oil Formula

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Casec®	75 Gm.	66 Gm.	1.5 Gm.	—	30 mgm.	45 mgm.
Salad oil	206 cc.	—	186	—	—	—
Distilled water	2150 cc.					
Tween 80®*	6 cc.					
(See below for salt supplement)						
Total volume	2400 cc.	66	187.5	0	30 mgm.	45 mgm.
Total calories	1952					

* Polyoxyethylene^{20} sorbitan monoöleate, manufactured by Atlas Powder Co.

TABLE III

Diet 3—Casec,® Oil Formula

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Casec®	170 Gm.	149.6 Gm.	3.4 Gm.	—	68 mgm.	102 mgm.
Salad oil	206 cc.		186			
Distilled water	2080 cc.					
Tween 80®	6 cc.					
		150	190	0	68	102
Calories	2310					

Diet 2 (Table II)

Method of Preparation

The "Tween 80®" is added to 600 cc. of water and the mixture homogenized in a blender. This homogenate is divided into three equal portions. To each portion is added one-third of the Casec® and enough water to bring to "half level" in blender. During blending, one-third of the oil is added. This is repeated for the remaining portions, and all are combined, using the balance of water for rinsing. The entire mixture is refrigerated.

TABLE IV

Diet 4—All Fat Formula

Food	Quantity	Protein	Fat	COH
Salad oil	240 cc.	—	216 Gm.	—
Distilled water	2160 cc.			
Tween 80®	10 cc.			
Calories	1944			

Diets 3 and 4 (Tables III and IV)

Method of Preparation

Identical with that for Diet 2.

TABLE V

Diet 5—Casec,® Oil (Cocoa Flavored)

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Casec®	45 Gm.	39.6 Gm.	0.9 Gm.	—	18 mgm.	27 mgm.
Salad oil	202 cc.		182			
Cocoa paste	210 Gm.	3.7	7.5	13	1566	1.6
Sucaryl® tablets	10				0.8	49
Vanilla	60 cc.				0	1.8
Distilled water	1000 cc.					
Tween 80®	4 cc.					
Total calories	1934	43.3	190.4	13	1584.8	79.4

Preparation of Cocoa Paste

	Quantity	Protein	Fat	Carbohydrate
Cocoa	100 Gm.	9 Gm.	18 Gm.	31 Gm.
Distilled water	400 cc.			

Cook in double boiler three hours.

Formulae for Oral Feeding

Diets 5 and 6 (Tables V and VI)

Method of Preparation

To weighed cocoa paste add crushed Sucaryl® tablets and vanilla. Proceed as for fat-Casec® formula (Table II), adding cocoa paste mixture. Save water for final rinsing. Refrigerate.

Diet 7 (Table VII)

Method of Preparation

Dissolve coffee and Sucaryl® tablets in a portion of hot water. Thereafter the preparation is as for Diet 6.

Diet 8 (Table VIII)

Method of Preparation

As for other oral feedings, using Kaolin instead of Casec.®

TABLE VI

Diet 6—Casec,® Oil (Cocoa Flavored)

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Casec®	114 Gm.	100.3 Gm.	2	—	45.6 mgm.	68.4 mgm.
Salad oil	170 cc.		153			
Cocoa Paste	210 Gm.	3.7	7.5	13	1566	1.6
Sucaryl® tablets	10				0.8	49
Vanilla	60 cc.				0	1.8
Distilled water	1000 cc.					
Tween 80®	4 cc.					
Calories	1935	104	162.5	13	1612.4	120.8

TABLE VII

Diet 7—Casec,® Oil (Coffee Flavored)

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Casec®	114 Gm.	100.3 Gm.	2 Gm.		45.6 mgm.	68.4 mgm.
Salad oil	190 cc.		171			
Sucaryl® tablets	8				.6	39
Powdered coffee (Borden's)	20 Gm.				1169	100
Tween 80®	6 cc.					
Distilled water	1000 cc.					
Calories	1958	100.3	173	0	1215.2	207.4

TABLE VIII

Diet 8—Oil, Kaolin (Cocoa Flavored)

Food	Quantity	Protein	Fat	COH	Potassium	Sodium
Oil	222 cc.		200 Gm.			
Kaolin*	75 Gm.					
Cocoa Paste	210 Gm.	3.7	7.5	13	1566 mgm.	1.6 mgm.
Sucaryl® tablets	10				0.8	49
Vanilla	60 cc.				0	1.8
Tween 80®	4 cc.					
Distilled water	800 cc.					
Calories	1940	3.7	207.5	13	1566.8	52.4

* Kaolin, an inert substance, acts as a stabilizer and gives body to the oral formula in the absence of Casec.®

Vitamin tablets containing a minimum of the following ingredients were given daily to all patients on tube or oral formulae:

Vitamin A—7500 u.
Vitamin C—150 mg.
Vitamin D—1200 u.
Thiamine—7.5 mg.
Riboflavin—6 mg.
Niacinamide—45 mg.
Pyridoxine—1.5 mg.
Calcium Pantothenate 7.5 mg.
Vitamin E—3 mg.
Iron—22.5 mg.
Manganese—9 mg.
Iodine—0.15 mg.
Copper—1.5 mg.
Calcium—300 mg.
Phosphorus—225 mg.

To the Casec®-oil feedings and the all-fat feedings, mineral supplements were added as follows:

1. Calcium lactate—1 Gm. three times a day to "all fat" feeding.

2. Standard salt solution No. 1—composition: 3 Gm. potassium phosphate, 3 Gm. potassium chloride, 1 Gm.. sodium sulfate per 50 cc. Dosage—50 cc. per day.

3 Salt solution No. 2—composition: 1 Gm. magnesium sulfate per 10 cc. Dosage—10 cc. per day.

In addition to the formula, patients may receive distilled water on the basis of individual requirement.

The intervals at which the oral diets are administered will depend upon the specific metabolic program. In our hands, these diets have usually been administered throughout the period 8:00 a.m. to 8:00 p.m.

Discussion

The foregoing formulae are prototypes of an infinite variety of diets which may be used, the specific composition depending upon the relative amount of protein, fat, and carbohydrate which one wishes to administer, and upon the total number of calories which are indicated.

During the past eighteen months, twenty-eight patients have been maintained on the formula tube diets for periods ranging from several weeks to four months.

In the case of the orally administered diets, only one balance study has been carried out, the other formulae being administered to patients under semi-controlled study where constant dietary intake was required for both clinical and investigative purposes. Thirty-two such patients have been maintained on oral formula diets for periods ranging from several weeks to three and one-half months. We have been agreeably surprised to receive far fewer complaints than had been anticipated.

In the case of the "all fat" dietary intake it is obvious that prolonged administration of this type of diet through other than a tube approach would be impossible in most if not all instances. One patient was maintained on such a diet for a period of one month, clinical ketosis being prevented by the concomitant administration of corticotropin and cortisone.[4]

In Figure 1 are shown some of the data obtained in a typical balance study using this type of dietary intake. Because of the constancy of the intake, one may attach significance to somewhat smaller changes than would be possible with the usual rotating balance diet.

To obtain maximal constancy and to reduce

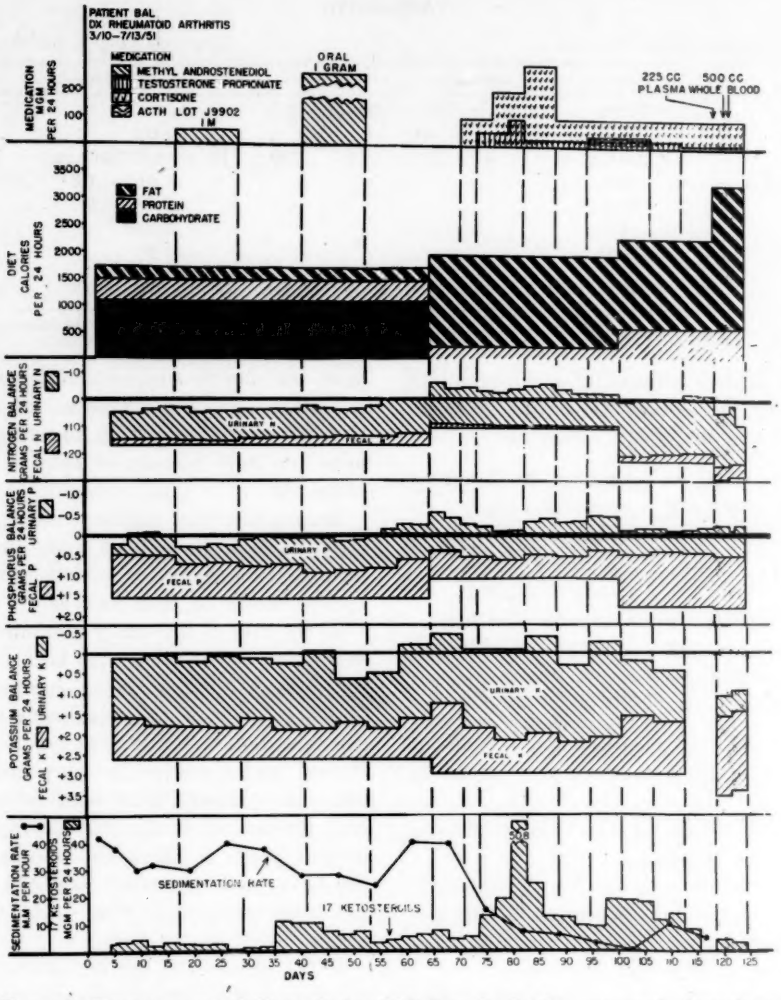

Figure 1—Long-term metabolic study in which formula intake was used throughout.

the number of quantitative determinations of dietary constituents to a minimum, large supplies of each material of identical lot numbers are kept on hand.

Summary

Over a period of eighteen months, sixty patients have been maintained on constant formula intake for periods ranging from one to four months. The use of this type of diet has the advantages of extreme constancy of intake and relative simplicity of preparation. The use of this procedure makes balance studies feasible in institutions where metabolic ward facilities are not available.

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Resumen

El uso de las dietas administradas a través de un tubo de politeno o por vía oral para los estudios de ingestión constante (equilibrio)

Durante 18 meses, por periódos de 1 a 4 meses, 60 pacientes han sido mantenidos mediante la ingestión de una fórmula constante. El empleo de este tipo de dieta ofrece las ventajas de una constancia extrema de ingestión, y de la sencillez relativa del método de preparación. El empleo de este procedimiento rinde hacederos los estudios de equilibrio en institutos donde faltan los servicios de una sala especial para enfermos de metabolismo.

PSYCHOSOMATIC ASPECTS of DIETING

By EDWARD WEISS, M.D.*

WITH THE widespread adoption of the psychosomatic point of view, more and more attention is being paid to emotional factors in obesity. It is not strange that this should be so. Next to the state of the weather, there is hardly a topic of conversation mentioned as frequently as weight loss or gain. This applies not only to women but to men as well, particularly in the last two decades when the obesity problem has been stressed from a health standpoint as well as for appearance's sake. It is recognized that the latter factor is not confined to women.

Excessive weight brings people into conflict for several reasons. First, overweight makes people look older and less attractive from the standpoint of our national ideal of "good looks." Secondly, many people are aware that obesity may have something to do with the development of such diseases as diabetes, hypertension, and heart ailments. Then, of course, conflict occurs when they attempt to do something about it, for they would like to maintain an attractive figure without foregoing the pleasure of eating. In this they have often in the past been aided by some members of the medical profession, who blame the condition on "gland trouble" and give medication to correct this. To avoid the unpleasantness of dieting, patients are often given harmful drugs or injure themselves by overexercise.

In short, a condition which was once looked upon as a question of endocrine glands and calories is now regarded as a complicated problem in which family background—meaning attitude as well as constitutional factors—is important. In other words, while obesity may run in families, habits are just as important as genes. In this regard, as in so many psychosomatic problems, the question of pseudo-heredity is just as important as heredity itself. For example, children identify with their parents and unconsciously imitate them. Thus, patterns of behavior are laid down (including illness as one aspect of behavior) so early in life that we often attribute a disorder to heredity when, in fact, it is acquired. This is an involved problem and we cannot hope to separate constitutional and environmental factors with absolute precision.

Thus, some families are quite oral in their orientation to life. There is much talk of food in the household—good food and plenty of it has security value or reward value—so that a child growing up in such a family may overvalue food and eating. The mother often gives the child the feeling that if he doesn't get enough to eat something dangerous will happen to him. Everything about the offering and receiving of food is endowed with a high emotional value. When finally forced to restrict foods, the choice of diet is often injudicious, based on the weird notions of "food experts" in popular magazines.

EMOTIONAL SIGNIFICANCE OF FOODS

In a paper devoted to food and allergies, Kaufman[1] pointed out that foods can be classified according to their emotional significance to the individual. "Most of us have at one time or another used certain foods in larger amounts than usual when we felt some special need to have emotional security. These are the 'security' foods. For example, in times of severe stress many persons unconsciously find it necessary to increase their intake of milk and milk products. Such persons often ration-

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alize their need for milk as eating 'lightly,' that is, not putting too great a load on their stomachs. But milk used in this way often symbolizes a strong desire to regress to the days when major decisions were made by the parents.

"We have also certain specific foods which serve us as 'reward' foods. If we are thwarted and frustrated, or if we feel that others have not appreciated sufficiently achievements which we accomplished through great effort; or if others fail to commiserate us sufficiently on our failures, we tend unconsciously to eat 'reward' or 'party' foods. We are good to ourselves by eating more chocolate, more ice cream, more nuts, more hot dogs, more cake—or perhaps we indulge ourselves in a tin of caviar.

"Certain foods seem to be used as 'fetish' foods—these are the ones which we think we can't do without. Some persons feel that unless they have red meat in their diet, they won't have the strength to carry on with their daily work; and others feel the same way about bread, the staff of life. It is quite common for people to feel that if they diet they will become weak and often when they succeed in losing a few pounds, some 'kind friend' puts a stop to the effort by telling them how 'awful' they look.

"Then there are the 'pleasurable association' foods. Sometimes, we eat certain foods because they remind us of people we like or of specific happy circumstances. Then, we have the 'grown-up' or 'maturity' foods like coffee, tea, beer, etc., which were 'for adults only' when most of us were children. Many individuals deprived of these foods as children, make overdetermined use of the 'grown-up' foods later when they become grown up chronologically.

"On the other hand, we have our private list of foods with which we have *unpleasant associations*. These include conditioned aversions, for example, the flesh of various pet animals which are said to constitute man's best friends. Then, there are foods to which we develop aversions through religious training or through cultural upbringing. We have taboos against eating nutritious and wholesome foods which we consider culturally as coming from filthy sources. In addition, we develop certain aversions because we associate certain foods with the onset of some acute illness that we experienced in the past. Or the food unconsciously reminds us of some unpleasant circumstance associated with its use, or perhaps it was the favorite food of some person we dislike intensely. Foods pleasurable in one form may be unpleasurable in another form. Then, we develop certain aversions to foods that have built-in conflict and anxiety associated with them. 'You must eat spinach,' when not to eat spinach is to defy parental authority, and to eat spinach is 'knuckling under.' Some aversions to wholesome foods operate on this infantile level—and some husband-wife conflicts are touched off when the wife serves spinach and urges her husband to eat it.

"Each individual has developed very early in his life conditioned responses to eating and to certain foods. His conditioned patterns of reacting are his individual integration of behavior he has learned from his culture, his religion, his parents (particularly the mother), and from his own life experience.

"The whole eating process is, moreover, a special training process by which the growing infant learns to accept various restraints and to live by certain conventions; 'baby must eat his meat before he can have his ice cream.' Food is used as a reward for achieving certain desired behavior patterns in the learning process. It is also used punitively and hostilely. Mother righteously tries to feed baby or child a food that she knows he despises—and then spanks him for not eating it, compounding the punishment. Eating, restraining of personal liberty, and punishment are frequent associations which are so strong in the lives of some people that they have an aversion to all food, and eat merely to sustain life and regard the eating procedure as ugly and unpleasant, to be gotten over with as rapidly as possible. Those who have received kindly and understanding food training by a patient mother can derive special enjoyment from eating—the pleasurable associations of early training outweigh the restraints and punishments."

Food Instead of Emotional Sustenance

Excessive interest in feeding is an unconscious effort of the mother to treat her children well and to strengthen them for life's battles through food because of her weak emotional relationship to them. She is unable to give them the strength of her love. It is as if the desire to satisfy the child with abundant nourishment has been exaggerated by the mother's reluctance to give something of herself. She fails to make them independent and self-reliant through emotional strength but tries to make them grow strong through size alone. They are not taught to derive pleasure through learning, play, competition, and social contacts, but are kept overprotected and overindulged. The result is often a lack of ambition, poor social adaptation, unhappiness, and obesity.

The classic studies of Bruch[2] on 140 obese children and their parents emphasized these facts and pointed out others. Marked delay in ability and willingness to take care of themselves was noted in three-fourths of the children. A concurrent evidence of immaturity in emotional development was shown by the symptom of enuresis which occurred in 40 per cent of those studied.

Entrance into school marked the first opportunity for social contact in these children. About two-thirds of the group were considered physically inactive. Few of them made use of the opportunities for muscular exercise provided by the school playground. They remained isolated and without playmates. Even in recreational activities involving other than muscular exercise there was little indication of creative self-expression. The majority of them sought the "made" entertainment of movies and radio. Only a small number of parents had encouraged activity or initiative in other ways. In fact, their overprotection of the child was extreme, sometimes to the point of wanting to accompany the child to school and even to the classroom door to help him remove his outer clothing. It is small wonder that these children expected that everything would be done for them. Slow and awkward movements were thought to be due to lack of training games and other activities, rather than to any abnormality in the mechanism of transformation of energy.

In a study with Grace Touraine in relation to the family setting from which obese children come, Bruch[3] observed that in such families the amount of money spent for food was disproportionately large. The obesity was rarely a matter of concern to the parents, although concern over minor physical ailments was excessive. Many of the fathers were weak, unaggressive people with little drive or ambition. The mothers had suffered from poverty and insecurity in their own childhood. In only a few families was there marital happiness. At times there was open fighting and frequently contempt was expressed for the father by a domineering mother. The families were usually small in size. Seventy per cent of the children studied were either only children or youngest children. Half of the children were admittedly unwanted. Sometimes hostility was openly expressed by cruel punishment or shown through unreasonable and severe discipline. But the most conspicuous feature in the attitude to the obese children was inconsistency. Most prominent was an open display of protectiveness. But this seeming manifestation of devotion and affection was frequently like a thin veneer that barely covered the underlying insecurity in relation to the child. The fundamental rejection was compensated for by overprotection and excessive feeding. These contradictions were more frequently observed in mothers than in fathers.

Psychic Conditioning

Muscular activity had been associated with the idea of danger in these fat children. Hence the lack of muscular activity and excessive intake of food were both factors in obesity, to which social and emotional adjustment were intimately related. Of course, all obesity does not have its beginning in childhood. It may come on at any age. What that age will be is determined in many cases by the same factors that cause the onset of any neurotic symptom. When insecurity or need for affection and attention become more pronounced than the maturity of the person-

ality can cope with, anxiety appears. If the pattern of that personality has been set up so that oral gratification through eating allays anxiety, then obesity is likely to result. If this conditioning to excessive eating is great enough, obesity may occur in childhood. If the conditioning is only latent in the framework of the personality, indulgence in overeating may not occur until some stress makes itself felt later in life. For example, an adolescent moves to a new neighborhood or enters a new school. He (or she) fails to get off to a good start in making friends and entering into social activities. Denied such pleasures, he regresses to oral gratification, eats excessively, withdraws into himself, further limits his muscular activities, and as a consequence gets fat. More than likely the obesity will be blamed on "glands."

Nervous Hunger

Patients do not present themselves for psychological study because of obesity. But treatment of patients for other conditions has revealed valuable information regarding the matter of overweight. Either sex may use the eating process to allay anxiety or to gratify pleasure cravings which should be satisfied in other ways, as for instance through a better sexual and social adjustment. A nagging, intolerable sensation in the epigastrium often referred to as "nervous hunger" is symbolic of the emptiness of the emotional life.

It is not surprising that feeding and feelings should be related. Anyone who has observed an infant recognizes that he feels out the world with his mouth and that everything that he can lay his hands on goes into that aperture. Moreover, the feeding process of infancy becomes closely connected with the attitude of the mother or nurse. If the feeding process is associated with love, affection, and security, the child is apt to be content and the digestive processes normal, whereas if there are tensions, insecurity, and anger associated with the feeding process, disturbed patterns of gastrointestinal behavior are apt to be established which reassert themselves later in life when the individual meets life situations which reawaken old associations. Thus foods and eating are associated with high emotional values.

PSYCHOLOGICAL PROBLEMS IN DIETING

All of these considerations, of course, enter into the problem of dieting. For example, as Freed pointed out,[4] anything which increases the emotional tonus, such as sorrow, nervousness, irritability, anxiety, or an emotional upset, will further the desire for food and cause an increase in weight in many persons who have a tendency to be obese. This is shown by the following data. Five hundred consecutive patients who requested treatment for their overweight were asked the question: "When you are nervous or worried do you eat more or less?" Three hundred and seventy answered that they ate larger meals or ate more frequently, 95 of the remaining 130 answered that they did not believe that they ate more when nervous or worried, but that they did eat more when they were idle, bored, or tired. The remainder claimed that their appetites were always good, or that they just enjoyed food.

Now obviously all overweight patients are not going to consult psychiatrists. In the first place, they wouldn't do it, and in the second place, there aren't enough psychiatrists to go around. Moreover, this is part of the general medical approach, and minor psychotherapy, which should be part of the equipment of every physician practicing general medicine, is sufficient to deal with many of these problems. Freed has pointed out a number of superficial conditions that may be inciting factors in the urge to eat excessively. He mentions the child who is brought up in a family conditioned to large amounts of food, and to people who are entertained or who entertain to a great extent or are constantly exposed to rich foods and encouraged to overeat. He mentions escape from monotony and calls attention to people such as traveling salesmen, who may vary the monotony of their trips by frequent eating. Many people take in more food when they are idle, and although it is recognized that the confirmed alcoholic frequently goes without food, it must also be recognized that social drinking is often accom-

panied by too much food. In the latter instance, the several cocktails not only create a voracious appetite but take away the inhibitions against large food consumption. Then there are the people employed in restaurants or delicatessen stores who are forever "nibbling." Again Freed points out that people who are bedridden or whose activities are restricted by a disability such as a fracture or convalescence from a surgical operation may overeat while they are inactive.

Furthermore, he states that the glandular dysfunctions which result in overweight are hardly those which have been taught for years in medical schools, which teaching is reflected in the traditional treatment of obese patients by thyroid or injections of such preparations as pituitary extracts. In only rare cases is obesity of endocrine origin. Some glandular conditions may, however, indirectly lead to increased appetite. The two most common endocrine dysfunctions found to be associated with overeating are the climacteric, which results in an increased nervous tension and thus leads to overeating, and premenstrual tension, which also increases tension but which occurs only for about a week before menstruation. Puberty and pregnancy are conditions which commonly precipitate overeating through the development of anxieties, fears, and new drives. The administration of thyroid for the reduction of overweight is in the great majority of cases without an adequate scientific basis. Many patients may actually gain weight on thyroid therapy because their appetite becomes greater as the result of increased nervous tension induced by the medicament.

But all kinds of worries, tension, and frustration may lead to overeating, and sometimes the psychological disturbance is so severe that the eating is like an obsession—indeed, very much like addiction to alcohol. Patients often explain that they cannot restrain themselves from stuffing with food in spite of the fact that they suffer the most severe guilt reaction afterwards. Such people, in whom it is obvious that powerful unconscious mental factors are at work, had better be referred to psychiatrists for help. The lesser problems can be handled by the general physician if he utilizes the psychosomatic approach, that is, studies psychological factors as well as physical factors. First, a complete examination of the patient should be made in order to determine the presence or absence of organic disease and, at the same time, to assure the patient that you understand his problem before you attribute his overeating to "nervous hunger." If the nervous disturbance is of a temporary nature, reassurance, sedation, and discussion of current problems may be sufficient to overcome it. Where the emotional tension is due to deeper and stronger influences, more effort must be made to understand the family relationships, in an effort to determine the cause of the increased desire for food.

For example, a woman of forty-two, a large, soft, dependent, and passive creature, took care of her husband and his business as a mother would, and had few of the pleasures, satisfactions, and responsibilities of a wife. After several visits she volunteered the information that some six or eight years ago she discovered that her husband was having an extra-marital affair and that thereafter "she had let herself go." That is, she had given up trying to dress attractively and had eaten as she pleased. As a consequence, she gained a great deal of weight. It was obvious that when she was denied certain satisfactions in life she regressed to oral satisfaction and, as a result, she became very heavy and, of course, even less attractive to her husband. It was not too difficult to point this out and to hold out as the incentive for a strict reduction diet the possibility of regaining her interests in life and regaining her husband's interest in her.

The effect of psychotherapy without the use of calculated diets was studied by Nicholson.[5] Ninety-three patients were divided into the following four groups:

1. Thirty-eight patients were treated by superficial psychotherapy without calculated diets and without medication; the patients were offered a simple explanation of energy exchange and the caloric value of foods.

2. Thirty-five patients were given a calculated diet of 800 calories. An experienced

dietitian explained the diet and, when desired, further instructions were given on return visits. There was no medication, nor was any effort at psychotherapy attempted.

3. Ten patients were given 5 mg. of amphetamine sulfate three times a day. No psychotherapy was attempted and no calculated diet was offered.

4. Ten patients were handled as in Group 3, except that thyroid substance was administered instead of amphetamine.

All obese patients studied were found to have some type of psychoneurosis in varying degrees. Psychotherapy resulted in a higher percentage of successful results than was obtained from the other methods of attempted reduction. Nicholson concluded that both psychotherapy and the reëstablishment of proper dietary habits are essential for permanent weight reduction. Like others with neurotic problems, these patients backslide when they meet new emotional upsets, so that they must be educated in this respect and encouraged to seek the help of the physician before they get into trouble. Needless to say, the patient receives a great deal of encouragement from loss of weight and his confidence builds up as he reduces. Thyroid is practically never indicated and in spite of a low basal metabolic rate there is usually no deficiency of thyroid function. This has been stated so frequently that it hardly seems necessary to say it again, but there can be little question that there has been pronounced abuse of thyroid therapy.

Anorexia Nervosa

Another eating problem, the opposite of obesity, is anorexia nervosa, a clinical syndrome which has brought home to the medical profession the necessity for believing that a psychological background may be responsible for a physical disorder. Within the last few years a number of excellent papers on this subject have appeared in which the psychological background is emphasized. Prior to this time, the diagnosis of Simmonds' disease was almost invariably made whenever the syndrome of anorexia, emaciation, and amenorrhea was encountered.

In 1874, Sir William Gull[6] observed a disorder of young persons characterized by the following symptoms: emaciation, scaphoid abdomen, amenorrhea, and the appearance of old age. He noted the slow pulse and subnormal temperature, the equivalent of the depressed basal metabolism so frequently mentioned in case reports labeled Simmonds' disease. He made shrewd observations as to the psychic behavior of his patients. In particular, he noted their sense of well-being and their excessive activity in spite of extreme emaciation. He pointed out that this degree of activity would be impossible if the inanition were due to constitutional disease. After discussing hysteria, he chose the term anorexia nervosa as a name for the disease. He pointed out that all of the symptoms could be explained on the basis of the undernutrition which, in turn, was due to a "morbid mental state." This was a time when the function of the pituitary gland was unknown. It is remarkable that in spite of this clear description so much confusion still exists in regard to this disorder.

Simmonds' Disease

At about this period of medical history, many morbid states which had been considered to be of psychological origin came under the influence of the new cellular pathology, with its structural orientation, and from then on they were considered of physical origin. Moreover, the recent interest and activity in the field of endocrinology has been a further reason for including this syndrome among the endocrine disorders. Simmonds in 1914[7] described the destruction of the anterior lobe of the pituitary gland which he observed at autopsy in certain cases of cachexia, and reconstructed from the history the clinical picture of the disease that now bears his name. The syndrome is a chronic, progressive disorder characterized by loss of weight, asthenia, atrophy of the genital organs with decreased sexual function (in women, amenorrhea—in men, impotence), loss of the axillary and pubic hairs, changes in the skin, and decreased metabolic rate. Hypotonia, hypothermia,

bradycardia, hypoglycemia, gastrointestinal disorders, anemia, and achlorhydria may also appear. Cachexia is a late phase of the disease. The pathologic changes, besides those already mentioned, are atrophy of the pituitary, skin, sexual glands, thyroid, parathyroids, and adrenals. In advanced cases, the internal organs are atrophied.

Differential Features

While the clinical picture of anorexia nervosa may reproduce all the symptoms of true Simmonds' disease, the changes usually are not nearly so marked as in the true pituitary cachexia, and autopsy observations prove that the pituitary is structurally intact. Recently McCullough and Tuffer[8] demonstrated an increased gonadotropic hormone excretion in some cases of anorexia nervosa, a finding inconsistent with severe pituitary failure.

Functional Pituitary Depression

From a psychological standpoint, it has been said that "just as these patients are physically starved, so are they emotionally starved." I would put it the other way around, because we must be very careful, in the consideration of psychosomatic disorders, not to put the cart before the horse. In other words, anorexia nervosa differs from true pituitary disease because it is the psychological conflict which brings about the loss of appetite and undernutrition and, very likely, this in turn affects the pituitary function, which is closely tied up with the cessation of menstruation and lowered basal metabolism. It seems that this is a true interference with the function of the anterior pituitary, but the latter occurs as a result and not as a cause of the disorder. One piece of evidence to suggest that this is a functional depression is that, when the patients improve as a result of psychological management, their menses begin again and even pregnancies may occur.

Nemiah's[9] well-studied series of 14 patients from the psychiatric service of the Massachusetts General Hospital leads him to conclude that the gastrointestinal component of anorexia nervosa should be considered not as just a loss of appetite, but rather as a disturbance in eating, ranging from true anorexia at one extreme to bulimia at the other, frequently associated with nausea and vomiting, and many other gastrointestinal symptoms. The finding of neurotic symptoms and traits preceding the onset of the syndrome lends support to the idea that patients with anorexia nervosa are not suffering from a simple, circumscribed illness involving appetite, weight loss, and amenorrhea, but are in a very wide sense maladjusted people.

Nemiah states that so frequently, despite the fact that emotional factors are invoked to explain the onset of symptoms, the approach to the problem is psychiatrically naïve. "Psychic trauma," "a foolish habit," "slimming," or "stubbornness" are suggested as etiological possibilities, and little attempt is made to observe and classify patients in terms of character traits, interpersonal relationships, and the other important elements of a thorough psychiatric history. It is only within the past years that psychiatric interest has been aroused and that psychiatric techniques have been applied to the problem of anorexia nervosa.

Psychic Traits

In all cases of anorexia nervosa studied psychologically there have been serious neurotic traits and sometimes even psychotic manifestations. Most patients showed a noteworthy reticence in discussing themselves and particularly in discussing sexual topics. In other words, there was a strong repudiation of sexuality, and if sexual relations occurred they often had a marked traumatic effect upon the psyche. In fact, starvation, emaciation, and the resulting unattractive appearance in many instances made an excellent defense against establishing healthy social contacts with the opposite sex. Sometimes this state of undernutrition led to the breaking of marriage engagements. Eating sometimes symbolizes impregnation to these people, and obesity represents pregnancy. Some of the other personality characteristics encountered are perfectionism, overconscientiousness, neatness, seclusiveness, shyness, and dependence upon others. Such patients have difficulty in mak-

ing friends and of necessity had a poor relation to parents. In many cases the parent had shown preoccupation with gastrointestinal functions and the patient as a child had been a "feeding problem."

Principles of Treatment

Treatment, then, consists in making the patient aware of the nature of the mental conflicts underlying the condition, and at the same time trying to reëducate the patient to express himself in a more adult fashion than by the rejection of food.

While the fully developed syndrome of anorexia nervosa is a rare disorder, lesser degrees of poor appetite and inanition based upon the same psychological principles are exceedingly common. As I have already pointed out, the taking of food is the chief activity during the first year of life and continues for some time to be connected in an important way with the child's entire relation to life. A mother who cannot understand the child's need for physical and emotional closeness to her may offer only food to the child. Parents often reward a child with something good to eat when some other reward would be more desirable psychologically. Thus it is that our relation to life starts through the feeding mechanism and may be continued almost exclusively through this channel. Appetite for food therefore becomes a substitute for and symbolic of an appetite for life activities. In all cases of anorexia nervosa we find the relation to life, usually expressed by enthusiasm for work, hobbies, and friends, to be as inadequate as the appetite for food. We can see that anorexia nervosa is a complex psychosomatic illness involving the whole personality, and the treatment can never be limited to the administration of tonics or endocrine products, but must include a study of the character of the person and his life situation.

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RESUMEN

Aspectos psicosomáticos de la adherencia a un régimen

El autor examina los factores emotivos que contribuyen al desarrollo de las transgresiones dietéticas resultantes en la obesidad, la delgadez, y varios trastornos funcionales.

Al lado de la obesidad hereditaria hay que considerar la posibilidad de una "herencia falsa," por la cual el hábito de la sobrealimentación resulta de la imitación por el niño de algun miembro de su familia, o de la adquisición temprana de una actitud que dota los alimentos de una importancia excesiva.

Según las teorías de Kaufman, ciertas categorías de alimentos representan "seguridad," "recompensa," o "madurez," mientras que otros alimentos tienen asociaciones más bien personales que los rinden o agradables o repugnantes. Los alimentos que significan "recompensa" y "seguridad" habrían de comerse en cantidad mayor en momentos de desgracia, conflicto, o contratiempo. Sirven de sustitutos a la seguridad emotiva, al amor, o al éxito.

Este sustituir de los alimentos puede ser iniciado por la madre, la cual, incapaz de dar a sus hijos amor o independencia, intenta "llenarles" el estómago. Falta de madurez,

un hogar desdichado, y padres demasiado solícitos (madres, sobre todo) son elementos que se encuentran con frecuencia en el ambiente de los niños obesos.

En adultos, ansiedad, nerviosidad, trastornos emotivos, monotonía, ociosidad, alcohol y embarazo pueden aumentar el apetito y el consumir de los que ya tienden a la obesidad. Hasta la administración de sustancias tiroideas con objeto de reducir el peso puede lograr el efecto contrario por el aumento de la tensión nerviosa producida por tal medicamento. En muchos casos, el médico puede ayudar a estos "adictos" a los alimentos con psicoterapía superficial; pero algunos habrán de ser enviado a psiquiatras.

En un estudio de Nicholson, a grupos de enfermos obesos se les dieron, repectivamente, psicoterapía superficial, un régimen reductor de peso, sulfato de amfetamina, o extracto tiroideo; la psicoterapía logró un porcentaje más elevado de resultados felices que cualquiera de los otros métodos.

En *anorexia nervosa* hay un conflicto psicológico que resulta en pérdida de apetito e hiponutrición, la que afecta, con probabilidad, la función pituitaria, con resultante cesación de la menstruación y disminución del metabolismo basal. El estudio psicológico de enfermos con *anorexia nervosa* ha revelado la presencia de condiciones neuróticas y aun psicóticas graves, a menudo de insatisfacción sexual. El tratamiento debe, por eso, incluir la resolución de los conflictos mentales responsables de la condición, y la reëducación psicológica del enfermo.

Editorial

What Is Nutrition?

In an attempt to define the limits of the field which this journal should cover, members of the Editorial Board were asked, in effect: "What is nutrition?"

To the surprise of practically no one, there emerged no boundary line which could be unanimously accepted. The cause lies not in our humble ignorance of so vast a science, but is inherent in the role of nutrition in all life processes. From the cataclysmic union of sperm and ovum, through intrauterine development, through birth, growth, maturity and simultaneous decline and senescence, through disease and injury, until at last vital forces are overcome and all metabolic activity ceases, the processes of nutrition are absolutely essential.

The very functions of life are completely dependent on energy, which in turn is derived from the combustion of foodstuffs. Growth and the unceasing process of repair depend on the utilization of protein and allied nutrients. The life of the individual cell is dependent on oxygen and water; but it is the iron-porphyrin-protein, hemoglobin, which carries the oxygen to the cell, and it is the ultimate breakdown of carbohydrate and interrelated nutrients which, with the fluids we drink, supplies the water. Enzymes and vitamins are the two sides of a coin; ubiquitous minerals come from the earth and from flesh to reach every cell.

As the branch of biology dealing with nutrients—substances ingested and necessary for the proper functioning of the body, nutrition is a large and vital part of all the medical sciences. At once cause and effect, it has no beginning and no end. Without adequate nutrition, there is disease, starvation, and death. With improper amounts or unbalanced combinations of nutrients, there are violent disturbances in every part of the body.

The ramifications of nutrition are universal.

Think of the obstetrician—he is concerned with the nutrition of the fetus through the mother, the anemias of pregnancy, the management of toxemias; the pediatrician—his greatest role is that of defender of good nutrition and hence of the normal growth and development of the child; the internist—he is preoccupied with nutrition as an essential in the management of the diabetic, hypertensive, cirrhotic, anemic, nephritic, the obese and the lean, the pellagrin, *ad infinitum;* the surgeon—he pioneered in recognizing the essentiality of fluid balance and nitrogen replacement; yes, and the geriatrician—for he holds out to the elderly the hope of happier years through sane eating. Why, all physicians are involved with nutrition, for it is not the disease that is important, but the person who has the disease—and each person is the product of his nutrition.

No one can foretell what future advances in this old, yet young, science will bring forth. How much closer to realization will be the happier, fuller life when the food supply of all peoples is adequate, when scientific progress, industrial efficiency and common knowledge have built for everyone the very basis of good health—good nutrition.

What is nutrition? It is the cornerstone of preventive medicine, the handmaiden of curative medicine, and the responsibility of every physician.

Dietotherapy

☆ *As a feature of immediate practical value to our readers, the* JOURNAL *will present a series of articles on dietetics by a noted authority, Corinne Robinson, Lecturer in Nutrition at Temple University, Philadelphia, and Chairman, Diet Therapy Section, American Dietetic Association*—ED.

FOOD THERAPY BEGINS WITH THE NORMAL DIET

THE MAINTENANCE or reëstablishment of good nutritional status is the fundamental objective of any dietary regimen. The principles which govern the planning of diets in health will likewise apply, in large degree, to the planning of therapeutic diets, inasmuch as the food requirements for most ill people are like those of people in health.

Disease conditions may greatly modify an individual's nutritive requirements. In some pathological conditions it becomes necessary to modify the normal diet with respect to the quantity of one or more nutrients. In other situations, qualitative changes, such as variations in consistency, flavor, and digestibility of food, are required. All such dietary modifications are most easily made when they are related to the normal diet. Moreover, if planning has been carried out in terms of the normal diet, it is a relatively simple matter to make an assessment of the nutritive adequacy of the modified regimen.

There is a distinct psychological advantage in relating all diets to the normal pattern. Even though considerable dietary modification is sometimes necessary for a short period of time, most people can look forward to a return to normal patterns of diet. Some people, of course, require modified diets for the rest of their lives, but even here emphasis can be placed on the *similarities to the normal diet* rather than on the deviations from the desired pattern.

What Is the Normal Diet?

No two individuals have absolutely identical food requirements. It is impossible to escape consideration of such factors as the individual's age, weight, activity, religious, social, and emotional patterns; nor can a dietary program become effective if there has been no regard to the cost and availability of food or to the facilities for properly cooking the food. The normal diet cannot be a "single rule of thumb" which can be applied to every individual.

The Recommended Dietary Allowances of the Food and Nutrition Board[1] provide a practical guide for planning normal and therapeutic diets. For example, the Recommended Allowances for a sedentary man or for a moderately active woman may be used to plan a foundation diet for persons in these categories. Such a *foundation* or Basic Diet is given in Table I. It will be noted that this diet provides ample amounts of all of the nutrients, but does not meet the caloric needs of most persons in these groups. Sufficient calories to maintain optimum body weight are obtained by eating larger amounts of any of the foods in the foundation diet or by adding cream, fats, sweets, desserts, etc., to this diet.

It should be emphasized that the basic diet is planned in terms of food classes rather than specific foods. Thus, the individual can fully express his preferences as to the kind of vege-

Nutritive Value of Basic Diet[2]

Food	Measure	Weight	Calories[1]	Protein[1]	Fat[1]	Carbohydrate[1]	Ca	Fe	Vitamins A	Vitamins Ascorbic acid	Vitamins Thiamine	Vitamins Riboflavin	Vitamins Niacin
		Gm.		*Gm.*	*Gm.*	*Gm.*	*Gm.*	*mg.*	*I. U.*	*mg.*	*mg.*	*mg.*	*mg.*
Milk or equivalent	3 cups	720	480	26	27	36	0.84	0.7	1,230	6	0.30	1.29	0.9
Meat, fish, or fowl[3]	3 ounces (raw wt.)	75 (cooked)	160	17	10	1	0.01	2.8	1,495	1	0.23	0.24	3.8
Egg	1	50	80	7	6	..	0.03	1.4	495	..	0.07	0.18	..
Other protein[3]	1 serving	50	90	6	6	3	0.05	1.1	205	..	0.08	0.11	0.4
Whole-grain or enriched bread	1 serving	30 (dry)	80	2	1	15	0.01	0.6	..	..	0.06	0.04	0.6
Whole-grain or enriched bread	3 slices	90	240	8	3	45	0.03	1.8	..	..	0.18	0.12	1.8
Potato	1–2 servings[4]	150	130	3	..	29	0.02	1.1	50	12	0.12	0.05	1.5
Green or yellow vegetable	1–2 servings[4]	150	50	3	..	10	0.14	2.1	6,225	44	0.13	0.22	0.9
Other vegetable	1 serving	100	30	1	..	7	0.03	0.5	265	14	0.03	0.03	0.3
Citrus fruit	1 serving	100	50	1	..	11	0.02	0.4	180	42	0.07	0.03	0.2
Other fruit	1 serving	100	55	1	..	13	0.01	0.4	740	11	0.03	0.04	0.3
Butter or fortified margarine	2 tablespoons	30	210	..	24	..	..	..	960	..	..	..	..
			1655	75	77	170	1.19	12.9	11,845	130	1.30	2.35	10.7[5]
Recommended Dietary Allowances—Woman			2400	60	..	..	1.0	12	5,000	70	1.2	1.5	12
Man			2400	70	..	..	1.0	12	5,000	75	1.2	1.8	12

[1] Calories have been rounded off to the nearest 5, and protein, fat, and carbohydrate to the nearest whole gram. In computing the averages for fruits and vegetables, the values have been weighted to conform roughly to the available food supplies.

[2] This assumes per two-week period: beef, veal, lamb, fowl—525 Gm.; pork, ham—300 Gm.; fish—150 Gm.; liver—75 Gm.

[3] Average of foods used for luncheon and supper dishes. Includes cheese, legumes, additional meat, or egg—small serving.

[4] It is assumed that 1–2 servings of potato and of green leafy or yellow vegetables will average 150 Gm. per day.

[5] The liberal tryptophan content of this diet together with this level of niacin will amply fill the niacin requirement.

tables, fruits, meats, and bread or cereals at any given time. Even though such broad classes of food permit a great deal of individual latitude in day-to-day meal planning, it should not be assumed that this is the only sound plan, or even the best one, which could be devised in any given situation. One could plan other diets which contained greater or smaller amounts of meat, cereals and breads, vegetables, fruits, milk, etc., and still achieve nutritive adequacy.

One of numerous ways in which the food allowances of the foundation diet can be arranged into a meal pattern is given below:

MEAL PATTERN	TYPICAL MENU
Breakfast	*Breakfast*
Fruit, citrus—1 serving	(Frozen) orange juice
Cereal, whole grain or enriched—½ cup	Wheat cereal with milk, sugar
Milk and sugar* for cereal	Soft cooked egg
Egg—one	Whole wheat bread
Whole grain or enriched bread—1 slice	Margarine—1 teaspoon
Butter or margarine—2 teaspoons	Coffee with cream, sugar
Beverage*	
Luncheon (or Supper)	*Luncheon*
Cheese, legumes, egg, meat, fish, or fowl—1 serving	Grilled cheese sandwich: bread, cheese, margarine
Vegetable, green or yellow, raw—1 serving	Mixed green salad
Salad dressing*	French dressing
Bread, whole grain or enriched—1 slice	Applesauce
Butter—2 teaspoons	Milk
Fruit—1 serving	
Milk—1 cup	
Dinner	*Dinner*
Meat—3 ounces	Tomato juice
Potato—1 serving	Meat balls with gravy
Vegetable—1 serving	Mashed potato
Whole grain or enriched bread—1 slice	Buttered carrots
Butter or margarine—2 teaspoons	Baking powder biscuit
Dessert*	Butter
Milk—1 cup	Tapioca pudding
	Milk

* These foods are in addition to the basic diet.

Milk may be used as beverage, for cereals, in soups, in milk desserts, etc. Butter or margarine may be used for flavoring foods as well as for a spread for bread; cream and salad dressing may replace part of the butter.

The Foundation Diet in a Program of Food Therapy

How can this or any other foundation diet be useful to the physician in planning the therapeutic diet?

To illustrate, let us suppose that a low calorie diet is desired. Reference to the Basic Diet in Table I makes it evident that a nutritionally adequate diet can be planned by using one or more of the following simple modifications depending on the desired calorie level: (a) use skim milk and decrease the butter or margarine; (b) reduce the amounts of bread, cereal, and/or potato but use whole milk; (c) include 1–2 extra servings of vegetables and fruit in order to provide extra bulk, better meal acceptability, and replacement of vitamins and minerals which are decreased by the reduced amounts of breads and cereals.

Again, what problems of nutritive adequacy would be encountered if a dietary program required the entire omission of milk? With the use of the calculated foundation diet it quickly becomes evident that milk contributes outstandingly to the protein, calcium, and riboflavin content of the diet, and importantly to the thiamine level of intake. Perhaps meat or eggs can be used in greater amounts to compensate for the protein supplied by milk, but these foods are not suitable substitutions with respect to calcium and riboflavin levels of the diet. Hard cheese is a desirable substitute for these valuable nutrients of milk, but in some situations such as the 200 mg. sodium diet is cannot be used. The physician then recognizes the need for prescribing supplements if the diet is to be used for more than a few days.

If, for example, raw fruits and vegetables are contraindicated in a certain clinical state, the use of all cooked foods may significantly lower the mineral and vitamin contributions of these classes of foods. Reference to the Basic Diet makes it apparent that one way to maintain the desirable ascorbic acid intake would be to double the amount of citrus fruit juice.

The physician who consistently evaluates the dietary regimens he prescribes in terms of

the normal diet will find that his patients accept his recommendations more willingly and are likely to abide by a program which permits individual food choice as well as suitable meal arrangements. Dietary modifications are less frequently made, because it is found that the normal diet is, after all, the most effective program in a great variety of situations.

The old-fashioned, dangerously inadequate, rigidly fixed "special" diet lists of years ago have no place in modern food therapy. They have given way to nutritionally adequate, individually acceptable therapeutic diets which use the normal diet as a foundation.—CORINNE ROBINSON

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Nutritional Quotes

Why Breast Milk?

"One accepts the fact that human milk taken by the infant from the mother's breast is the ideal food for the human infant: this needs restating, particularly at the present time, because it has recently been questioned, and figures have been published showing that small infants fed on a modified cow's-milk mixture with a high protein content, can achieve more rapid gains in weight than with breast milk. That this is so can be accepted, but it is salutary to remind ourselves that good nutrition cannot be determined merely by a gain in weight. Indeed, except for the very small premature infant in the first weeks of life, a too rapid gain may be disadvantageous: overweight infants succumb to infections more frequently than those who are of average weight for age."
—S. Graham. *The British Journal of Nutrition* 6: 207, 1952.

Intravenous Iron

"Iron should not be given intravenously to patients with refractory anemia because they are refractory on oral administration, but only to those who have a hypochromic anemia with iron deficiency. It should not be given in a quantity materially greater than is needed to replace this deficiency, as calculated from the amount of hemoglobin and the probable blood volume. With this precaution, intravenous administration of iron should be valuable in a small selected group in whom iron orally administered is disturbing or poorly absorbed, and in the later stage of pregnancy, when rapid replenishment of the iron stores is important."
—P.W.C., editorial. *Annals of Internal Medicine* 36: 699. 1952.

The Extrinsic Factor

"It appears, therefore, that the macrocytic anemia of tropical sprue or pernicious anemia is a multiple deficiency state, and that both folic acid and vitamin B_{12} are necessary to correct this abnormality of hematopoiesis. The synergistic action of folic acid and vitamin B_{12} (extrinsic factor), or vice versa, suggests the possibility that folic acid is needed for the proper absorption and utilization of vitamin B_{12} by the human organism.

The extrinsic factor as described by Castle may very well be a combination of substances, among which folic acid and vitamin B_{12} play a prominent role."
—F. Diez-Rivas, F. Hernandez-Morales, and L. M. Meyer. *Annals of Internal Medicine* 36: 1076, 1952.

Antibiotics and Vitamins

"More work is needed before any sound conclusions can be drawn concerning the mode of action of the antibiotics in influencing the requirements for known dietary factors. It is of course only speculation that an antibiotic apparently can conserve a given vitamin for the host by suppressing the intestinal organisms that are in competition with the host for that vitamin in the intestinal contents."
—*Nutrition Reviews* 10: 108, 1952.

It's the Milk, Not the Cereal

"It is unfortunate that some have seized upon the results displayed in recent literature to claim a nutritional superiority of one cereal over certain others. This practice is unwarranted, unethical, and not in the interests of the public good. Breakfast cereals are eaten with milk, only rarely with water alone. Any differences in the biologic value of their proteins is obliterated when consumed with the proper proportions of milk—a weight ratio of 1:1."
—*Nutrition Reviews* 10: 130, 1952

Nutrition and Aging

"The chronic disease problem and the aging of tissue are closely related. They are so important to this country and to the entire world that every effort should be made to understand them and bring them under control. Nutrition must be as important to the process of aging of tissue as it is to growth and development, yet only a very small beginning has been made in this field. Aging need not be synonymous with degeneration. Satisfactory nutrition throughout life has the best chance of making such a separation a reality."
—R. W. Vilter and C. Thompson. *Public Health Reports* 66: 636, 1951.

Modern Concepts of the Importance of Fat

"The novel position of importance achieved by fat in the continuing metabolism is an intriguing subject for speculation. The foremost point for consideration is that, except for the essential fatty acids, which have a purely operative role, fat is not altogether a separate foodstuff; it is equally an intermediary compound in the metabolism of carbohydrate. It is rather banal to state that this is one more good reason why more attention should be given to the metabolism of the lipids, both in physiology and the clinic. It is at least fair to suggest that the metabolism of the two foodstuffs should no longer be categorically separated. The glucose-fed animal, so dear to physiologists and biochemists, is not just what it used to be. Concepts of the role of glycogen require modification. It has already fallen far from the high estate it enjoyed in the reign of Hill and Meyerhoff, when it was the sole fuel of muscle. Is it now to be displaced from its position as the chief source of continuing energy? This possibility must at least be given open-minded consideration. An adult male, under ordinary conditions, does not develop ketosis of any important degree until he has starved 48 hours or more, although the glycogen in his body could supply his energy requirements for only a fraction of this time. After an overnight fast three-fifths of the energy production is sustained by fat. If it were not, the glycogen stores would be entirely exhausted."
—J. P. Peters. *The Yale Journal of Biology and Medicine* 24: 68, 1951.

New Method of Bone Density Measurement

"The photometric technic of measuring the density of bones which reflects their mineralization and, more specifically, their calcium status, has important applications in nutritional research. It may replace the tedious calcium balance technic and may provide information on the absolute status of mineralization rather than simply furnish a balance sheet of the difference between intake and output. It may provide a valuable tool for the study of changing calcium status in such conditions as pregnancy, and versatile means for the study of other factors which effect calcium metabolism, normal and abnormal."
—*Nutrition Reviews* 10: 124, 1952.

B Vitamins and Antibodies

"The available evidence would indicate that certain B vitamins, notably pyridoxine, pantothenic acid, and pteroylglutamic acid, play a significant role in antibody synthesis."
—A. E. Axelrod. Role of the Vitamins in Antibody Production, in *Recent Advances in Nutrition Research,* National Vitamin Foundation, New York, 1952, p. 27.

Diet after Total Gastrectomy

"A high caloric (50 or more calories per kilogram of body weight), high fat (200 to 250 grams), high protein (100 to 150 grams), low carbohydrate (200 to 250 grams) diet, taken in the form of numerous small meals is recommended following total gastrectomy for the attainment of the optimal nutritional status."
—T. C. Everson. *Surgery, Gynecology and Obstetrics* 95: 209, 1952 (Intern. Abstr. Surg.)

Nutrition Briefs

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

PYRIDOXINE deficiency led to the development of hypertension in albino rats. Pyridoxal supplementation led to weight gain and significant fall in blood pressure.

N. E. Olsen and W. E. Martindale. *Fed. Proc.* 11: 115, 1952.

UNDER CERTAIN experimental conditions, the amount of copper in the tissues influences the amount of iron absorbed.

M. S. Chase, C. J. Gubler, G. E. Cartwright, and M. M. Wintrobe. *Fed. Proc.* 11: 438, 1952.

SKELETAL aging in mice was found to proceed most slowly on a high protein *ad libitum* diet, most rapidly on a high fat diet, and at an intermediate rate on a high carbohydrate diet. Both the caloric intake and fat specifically influenced the rate of bone development and bone aging.

M. Silberberg, R. Silberberg, and M. Opdyke. *Fed. Proc.* 11: 246, 1952.

THE DISTRIBUTION of radioactive menadione (vitamin K, with C^{14} in the methyl group) was studied in mice. Forty per cent of the injected activity left the injection site in 15 minutes; about 60 per cent was excreted in the urine within 3 hours. Only a fraction of 1 per cent was found in the liver, muscles, skin, etc., and a maximal value of only 5 per cent was detected in the bile and intestines in 2–3 hours. Radioactive dicoumarol, however, is concentrated in the liver.

P. R. Solvonuk, L. B. Jacques, and J. W. T. Spinks. *Fed. Proc.* 11: 152, 1952.

ASCORBIC acid was found to be a factor in the oxidation of aromatic drugs, such as antipyrine, theophylline, acetanilide, etc.

J. Axelrod, B. B. Brodie, and S. Udenfriend. *Fed. Proc.* 11: 319, 1952.

ISOTOPICALLY labeled vitamin B_{12} (cobalt^{60}) apparently appears in the milk of rats, particularly if administered subcutaneously.

R. C. Ellingson, A. J. Mueller, W. M. Cox, Jr., and B. F. Chow. *Fed. Proc.* 11: 441, 1952.

RATS on a low protein, high fat diet were found to have an increase in the adrenal cholesterol content and diminution in the adrenal weight. These changes were not associated with an increase in serum or liver cholesterol. ACTH administration caused an increase in adrenal weight, indicating the adrenals were not refractory. Vitamin B_{12} had a distinct lipotropic effect on the liver, but adrenal cholesterol was not reduced.

H. Gershberg and E. P. Ralli. *Fed. Proc.* 11: 54, 1952.

CURRENT OBSERVATIONS OF CLINICAL INTEREST

A SURVEY of hemoglobin values in children in a Newfoundland boarding school showed a significant increase in the number of anemic children through the years 1948–1951. In 1949, all flour used contained 3 added vitamins and iron, plus 500 mg. of bone meal per pound of flour. In a control school in the same area, the frequency of anemia actually declined. If enriched flour caused the increase in anemia, this may be explained by an interference with iron absorption by the calcium of phosphate in the bone meal. If enriched flour did not cause this anemia, it is still significant that no beneficial effect was noted from the iron in enriched bread.

L. B. Pett. *Fed. Proc.* 11: 543, 1952.

PATIENTS with a sprue-like syndrome showed no increase in serum vitamin A after the oral administration of vitamin A ester and alcohol. On the other hand, patients with chronic pancreatitis showed no response to vitamin A ester, but had an increase in serum vitamin A following administration of the alcohol.

M. M. Kaser, R. Minton, and C. V. Hussey. *Fed. Proc.* 11: 238, 1952.

CAREFUL carbohydrate tolerance curves in obese and non-obese women, paired with respect to age and height, were performed. The results showed a wide spread in the obese and non-obese groups. Both categories contained some subjects who responded with an abnormal elevation in blood sugar, but the obese group showed on the whole a sluggish rise in blood sugar during the first half-hour.

T. B. Van Itallie, R. Beaudoin, and J. Mayer. *Fed. Proc.* 11: 547, 1952.

AN ANALYSIS of the food habits of 1072 Iowa women aged 30–90 years old revealed that the average daily calorie intake was 1700 calories, with an average protein intake of 57 Gm. Sixty per cent consumed less than 1800 calories. With advanced age, the average daily intake of all nutrients decreased.

P. Swanson, M. Ohlson, L. Burrill, A. Biester, J. Smith, and E. Batchelder. *Fed. Proc.* 11: 457, 1952.

THE PHYSIOLOGICAL responses of men over 60 years of age were altered by the omission of breakfast. The reaction time, neuromuscular tremor, oxygen required to work, and strength were found to be adversely affected when breakfast was omitted. On the other hand, the size and content of breakfasts studied had no effect in this age group.

W. W. Tuttle, K. Daum, and B. Randall. *Fed. Proc.* 11: 164, 1952.

METABOLIC STUDIES with S^{35}-labeled methionine reveal that patients with the nephrotic syndrome synthesize both albumin and globulin at greatly increased rates; the rate of urine excretion of albumin is identical with the rate of albumin synthesis and the S^{35} content of urinary protein is identical with serum albumin.

S. Margen, J. Lange, H. Tarver, R. De Laney, and L. Kinsell. *Am. J. Med.* 13: 97, 1952.

LIVER and dietary vitamin A concentrations are logarithmically related to plasma vitamin A.

H. J. Almquist. *Arch. Biochem.* 39: 243, 1952.

Nutrition News

☆ *News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the* JOURNAL.

GAMBIA CONFERENCE

Dr. Paul György and Dr. A. L. Maynard will represent the United States at a conference on nutrition to be held in Gambia, November 10–December 4, under the auspices of the World Health Organization and the Food and Agricultural Organization of the United Nations.

Dr. György is Professor of Nutrition in Pediatrics at the University of Pennsylvania School of Medicine. Dr. Maynard is Professor of Nutrition at Cornell University and Chairman of the National Research Council Food and Nutrition Section.

NUTRITION PROGRAM FOR PENNSYLVANIA

In an effort to disseminate current advances in applied nutrition to physicians and public alike, the Medical Society of Pennsylvania created a Commission on Nutrition, which has been active on several fronts. The following brief summary of this Commission's activities should prove interesting to other groups charged with similar duties.

To reach the general practitioner, the Commission has prepared editorials on various phases of nutrition for insertion in the state medical journal. Over the past two years, fifteen of these have appeared.

Exhibits, designed to dramatize nutritional problems, are another Commission project. At the 1952 State Convention, an exhibit on obesity was presented, accompanied by five-minute speeches on the association of obesity with various diseases and as a public health problem. A year ago, at its annual session, the State Medical Society held a Symposium on Nutrition, in which the Commission participated. County societies have been asked to cooperate with the Commission by giving nutrition a place in their publications and on their programs. Local societies may apply to the Commission for a list of available subjects and speakers. The Commission has successfully urged that nutrition be incorporated in the Postgraduate Program offered annually by the State Medical Society, where its inclusion should help awaken physicians to the importance of this indispensable requisite to total medical care.

For hospitals without dieticians, a manual of standardized diets is being prepared for statewide distribution.

Seeking greater unity of effort in the field of nutrition, the Commission has organized a Coordinating Committee on Nutrition, its members representing all the major agencies concerned with nutritional problems.* The object of the Coordinating Committee is to pool and check all available information and to participate jointly in all approved projects.

One of the first problems considered by the Coordinating Committee was the suspected lack of emphasis on nutrition in interne education. Answers to a questionnaire, sent to all approved internship hospitals in Pennsylvania, confirmed the Committee's belief that a brief, formal period of nutrition instruction is needed if internes are to emerge from their training with a clear understanding of nutritional problems and an adequate knowledge of available therapeutic diets.

It was felt that the rather rigid separation of the medical and dietetic staffs which prevails in most hospitals should be broken down. Greater emphasis on nutrition in internship training would be one way to accomplish this. Ideally, this training should be given in the

* Commission on Nutrition, Medical Society of the State of Pennsylvania; Division of Nutrition, State Health Department; Pennsylvania Dietetic Association; Lankenau Hospital; Committee on Nutrition, Philadelphia County Medical Society; Pennsylvania State Dental Society; Pennsylvania State Nurses Association; Division of Physical Education, Department of Public Instruction; Committee on Nutrition of the Philadelphia Council of Civil Defense.

hospital's nutrition clinic; where none exists, it would be the responsibility of the dietetic department. The Committee also suggested that a member of the dietetic department should accompany physicians and surgeons on their ward rounds.

Dr. Michael G. Wohl, Chairman of the State Commission and the Coordinating Committee on Nutrition, while pleased with its past accomplishments and hopeful of its present undertakings, looks forward to the time when physicians will become more enthusiastic missionaries in the cause of nutrition, the public more intelligent converts.

Reviews of Recent Books

Carbohydrate Metabolism. A symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease edited by V. A. Najjar, Johns Hopkins Press, Baltimore, 1952, pp. 134, $4.00.

This short book is a collection of presentations made at a symposium on carbohydrate metabolism. The authoritative nature of the material may be surmised from the list of discussers, i.e. such investigators as Cori, Hastings, McQuarrie, Butler, and Andersen, among others. Most presentations deal in a clear style with problems *in vitro;* however, certain important clinical observations are also noted. Familial hypoglycemia (associated with absent alpha cells of the islet tissue) and a laboratory differentiation of three types of glycogen storage disorders are described. Recent advances in enzyme and electrolyte metabolism are nicely summarized. There is a useful index.

This book offers a brief review of current research in medicine and physiology dealing with carbohydrate metabolism, and will prove useful to clinicians and research workers alike. S.O.W.

Phosphorus Metabolism. A Symposium on the Role of Phosphorus in the Metabolism of Plants and Animals. Volume I, edited by William D. McElroy and Bentley Glass, The Johns Hopkins Press, Baltimore, 1951, pp. 762, $10.00.

The functions of phosphorus in nutrition are numerous and important. Investigations carried out during the past 25 years have provided new concepts of its role in metabolism. Great progress has been made in describing the intricate metabolic pathways by which phosphorus facilitates the degradation of metabolites and aids in the transfer of energy released thereby. The contributions of the last few years especially have added such an abundance of new information about the interactions of phosphorus that a comprehensive survey of recent work was badly needed. The more than 40 papers comprising the Symposium on Phosphorus Metabolism held at Johns Hopkins University in June 1951 help greatly to fulfill this want. This volume gains authority because many of the participants actually discuss the outstanding contributions they have made in this field.

The topics discussed include the metabolism of polysaccharides, the metabolism of hexoses, pentoses, and trioses, the formation and utilization of active acetate, the structure and reactions of phosphorus-containing coenzymes, the biochemistry of inorganic pyro- and meta-phosphates, the influence of inorganic ions on phosphorylation reactions, the thermodynamics of phosphate bonds, coupling of oxidative phosphorylation and electron transport, and utilization of phosphate bond energy. There is an introduction to the Symposium by the late Professor Meyerhof and a comprehensive 83-page summary and review by Professor Bentley Glass.

This is an important book. Much of the information it contains is not available elsewhere, and if so could be collected only by considerable effort. These discussions of active acetate and of the manifold reactions of coenzyme A serve as an excellent introduction to this rapidly expanding subject. Numerous other examples could be cited. The ramifications of phosphorus metabolism are sufficient to warrant inclusion of sections on urea formation, synthesis of peptide bonds, transmethylation, bioelectricity and bioluminescence. An index is included. J.G.R.

Copper Metabolism, edited by William D. McElroy and Bentley Glass, The Johns Hopkins Press, Baltimore, 1950, pp. 443, $6.00.

This is a monograph which covers a group of papers presented at a symposium held at the McCollum-Pratt Institute of Johns Hopkins University on June 14, 15, and 16, 1950, on Copper Metabolism. This is the most authoritative, comprehensive and up-to-date treatise in the field dealing with copper metabolism from the standpoint of animal, plant, and soil relationships. Such chapters as The Copper Protein, Ascorbic Acid Oxidase, The Nature of Copper Enzymes Involved in Tyrosine Oxidation, The Use of Radioisotopes of Copper and Molybdenum in Nutritional Studies, Problems Associated with Copper Deficiency in Ruminants, and Copper Metabolism in

Human Subjects, are written by specialists in micronutrients from the United States, Australia, and New Zealand. This book should prove a most valuable reference to all graduate students and investigators in nutritional biochemistry.

Space does not permit to comment on the contents of the individual chapters. However, the following are some of the vital points covered in the chapter on Copper Metabolism in Human Subjects which should be of interest to the clinical and practising physician. In the adult, whole blood contains about 94 micrograms of copper per 100 ml. which is distributed equally between cells and plasma. The copper in plasma increases in most infections, including pharyngitis, and the "common cold." The presence of hypercupremia has been suggested as a delicate test for the detection of infection. In chronic infections, such as tuberculosis, osteomyelitis, empyema, lung abscess, subacute bacterial endocarditis, and brucellosis either with or without anemia, the plasma copper is almost invariably elevated to levels of 160 to 250 microgram per cent. As soon as the acute phase of the infection subsides, the plasma copper decreases to normal.

Increases in whole blood and plasma copper have been observed in various types of malignancy and in acute leukemia. A favorable response to the administration of adrenocorticotrophic hormone in acute leukemia is accompanied by a decrease in the copper values, and relapse is accompained by an increase in the copper values.

Pregnancy is one physiological condition in which the blood copper content is greatly altered. In the 40th week of pregnancy, the plasma copper averages about 261 microgram per cent. The plasma copper begins to increase in the sfirt trimester and reaches maximum values during the last trimester. Normal values are then regained rapidly during the first two months post-partum.

The function of copper in mammals is not known. From the results of studies in copper-deficient animals, the indications are that it is concerned in erythropoiesis, in the process of myelinization of the central nervous system, and in the maintenance of normal mammalian pigmentation. In what manner copper functions in these ways is not understood.

B. SURE

Food and Nutrition by E. W. H. Cruickshank, M.D., Ph.D., M.R.C.P., second edition, The Williams and Wilkins Company, Baltimore, 1951, pp. 443, cloth $6.50.

This book consists of twenty chapters, dealing with the usual subjects generally considered in books on nutrition, in addition to a wealth of material on the practical application of nutrition findings on the individual, the family, the community, the nation, and the world. In the chapter on bread, Dr. Cruickshank traces the history of bread-making from prehistoric man to the so-called "National" loaf which is mandatory today in Great Britain. He relates the many shortcomings of modern white bread, the reasons why current methods of milling have come about, and the whole story of flour bleaching and "enrichment."

Although quite conservative in his thinking on, for instance, natural versus processed food, vegetarianism versus meat-eating, wrong diet versus salivary bacteria as the cause of tooth decay, the author is always fair in pointing out that perhaps further research will reveal additional significant facts on one side or the other of these various controversies.

Perhaps the most striking aspect of the book is its international flavor. Although Dr. Cruickshank is mainly concerned with Great Britain and her food and nutrition problems, he is thoroughly acquainted with the food situation in other parts of the world as well. His comparative statistics on African nations with widely differing diets reveal the tremendous importance of food as a determining factor in a nation's physique, philosophy, and temperament. His very thorough review of how Great Britain faced and solved her nutrition problems during the last war contains much of value for American nutritionists and physicians.

In general, the author is fully aware that all is not well in regard to nutrition, even in countries where the standard of living is high. His recognition of this fact is apparent in the theme of the book—that technical development and scientific knowledge must be closely related if we are to solve our nutrition problems and bring about a healthy and stable peace. In short, this is a good, well-rounded treatment of all aspects of food and nutrition. J.R.

Internal Medicine (fifth edition), formerly edited by John H. Musser, B.S., M.D., F.A.C.P., now edited by Michael G. Wohl, M.D., F.A.C.P., Lea & Febiger, Philadelphia, 1951, pp. 1563, $15.00.

Textbooks of general internal medicine must cover a vast amount of material, yet be concise, pertinent, current, and (most difficult of all) readable. Such a combination, happily, is found in the new (fifth) edition of Musser's textbook of Internal Medicine, now edited by M. G. Wohl, and with contributions from 81 authors.

Although the presentation of the disease entities is orthodox in that for each condition there is a section on etiology, pathology, diagnosis, treatment, etc., the book emphasizes patho-physiology and prevention. There are interesting integrating chapters at the beginning of each large section, as well as well-written chapters on geriatrics, rehabilitation, genetics, the alarm reaction, and psychosomatic medicine.

The chapters on nutrition were contributed by several members of the Board of the JOURNAL OF CLINICAL NUTRITION. Throughout the book the discussions

are clinical, well illustrated, and surprisingly up-to-date, with references from 1951.

The book is attractively printed, with a useful index. It can be unhesitatingly recommended as one of the best in its class available today. A.E.S.

Alcohol Education: A Guide-book for Teachers by Joseph Hirsh, Henry Schuman, Inc., New York, 1952, pp. 107, $2.50.

Our laws require the teaching of the "facts" about alcohol in the schools of all 48 states. But what is taught and how the instruction is slanted depend to a great extent on local attitudes and on the preparation and prejudices of the teacher. This guide to alcohol education is designed to help teachers acquire the facts about alcohol, answer the most common questions asked about its nature and action, understand the special problems associated with the disease of alcoholism, and plan a rational and realistic program of alcohol instruction. As the author points out, eager advocates of abstinence may insinuate into the teaching program a distorted "scare" picture of the evils of alcohol, which the pupil finds difficult to reconcile with what he sees about him in our predominantly drinking society. Rejecting the distortions, he may ignore the real dangers which accompany the use of alcohol—such as combining even moderate drinking with driving, or overlooking the early signs of alcoholism.

The real and fancied properties of alcohol are discussed. Is alcohol a food? A stimulant? A narcotic? In what sense is it habit-forming? Can it cause specific diseases? Has it any medicinal value? The differing response to alcohol in the youthful and older drinker is stressed, and a careful distinction is made between the ordinary "social" and the potential "problem" drinker. The author is frank about the residue of unknowns in our accumulated knowledge about alcohol; he points out, for example, that the relation of alcohol to nutrition needs to be explored more thoroughly.

A list of agencies interested in alcohol education is included; and evaluations of available films and filmstrips on various aspects of alcohol and related problems, together with a selected bibliography, should prove helpful to teachers and administrators in search of source material and visual aids.

In making this guide available, the author has made a practical contribution toward the establishment of a program for alcohol education more firmly based on medical, psychological, and sociological knowledge. C.-J.H.

The Complete American-Jewish Cook Book, edited by Anne London and Bertha Kahn Bishov, The World Publishing Company, Cleveland and New York, 1952, pp. 752, $4.95.

This cook book offers over 3500 recipes of kosher dishes, plus a large amount of interesting folklore. Profusely illustrated and covering the gamut of Jewish cooking, this book should prove popular with gourmets and housewives of all faiths. S.S.

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Biochemistry and Human Metabolism by B. S. Walker, W. C. Boyd, and I. Azimov, Williams & Wilkins Co., Baltimore, 1952, pp. 812, $9.00.

Freezing and Drying, edited by R. J. C. Harris, Hafner Pub. Co., Inc., New York, 1952, pp. 205, $3.00.

The Inspection of Food: A Handbook for Students of Public Health, Agriculture and Meat Technology by Horace Thornton, Williams & Wilkins Co., Baltimore, 1952, pp. 223, $3.00.

The Newer Knowledge of Hygiene in Diet by J. Sim Wallace, Dental Items of Interest Pub. Co., Inc., Brooklyn, 1952, pp. 264, $4.75.

Essentials of Infant Feeding for Physicians by Herman Frederic Meyer, Charles C Thomas, Springfield, 1952, pp. 252, $6.75.

Manual of Applied Nutrition, edited by J. C. Carlsen, Johns Hopkins Press, Baltimore, 1952, pp. 96, $2.50.

Kitchen Strategy by L. M. Bayer and E. Green, Charles C Thomas, Springfield, 1952, pp. 112, $3.75.

B-Vitamins for Blood Formation by Thomas H. Jukes, Charles C Thomas, Springfield, 1952, pp. 113, $4.00.

Abstracts of Current Literature

DIABETES

Diabetes mellitus is intimately related to nutrition in many of its aspects, from pathogenesis of the disease, and the incidence of certain complications, to dietary treatment. With respect to recommendations for diets to be prescribed in diabetes, considerable differences of opinion are voiced by various authorities.

Further Observations on the Use of Liberalized Diets in the Treatment of Diabetes. H. J. John. *Ann. Int. Med.* 35: 1318, 1951.

This is an account of the author's personal experience with a simplified liberal dietary management of diabetics. He does not feel that detailed planning and weighing of food is necessary in many instances. The psychologic problem so induced may be detrimental to the patient. Instead, he prescribes a "normal" diet (2000 to 2500 calories), with the patient eliminating sugar, pastry, and soft drinks, and restricting bread to 2 slices or less per week. Fresh fruit or cheese and crackers are substituted for dessert. The weight is used as a guide to total caloric intake. Ten cases are reported, in which insulin was either discontinued or reduced while the diabetic was controlled by this liberal regimen.—S. O. WAIFE

In contrast to the liberal character of the diet suggested in the above is the finding of a higher incidence of degenerative complications in poorly controlled patients, which has led the author of the following paper to recommend more careful attention to dietary regulation.

Degenerative Complications of Diabetes: A Review. H. F. Root. *J. Clin. Endocrinol. and Metab.* 12: 458, 1952.

The effect of diabetes mellitus upon the nervous tissues, the arteries, the retinal vessels, and the kidneys is reviewed in this comprehensive paper. The feeding of diets relatively high in protein and sufficient in caloric content to maintain the patient at ideal weight (so as to correct obesity if present) is strongly urged. In diabetic neuropathy, the use of vitamin B_{12} has been found effective only in a limited group of patients. In about 50 per cent of patients treated with BAL a favorable effect was observed on the neuropathy.

It is of interest that no patients with excellent or good "control" were found to have advanced retinitis, vascular disease, or diabetic nephropathy after prolonged diabetes. A large majority of diabetics on an unmeasured diet with poor control over a period of 20 years showed marked degenerative vascular disease. The occurrence of hyaline changes in the vessel walls of the retina, glomerulus, and elsewhere is related to metabolic disturbances in the mucopolysaccharide complexes. It appears that the careful regulation of diabetes may be important in preventing these pathological alterations.—C. R. SHUMAN

Following recovery from diabetic coma, the initial diet offered to the patient is an important, yet oft-neglected factor.

Feeding of Patients after Termination of Insulin Coma Treatment. E. Revitch and R. Harshfield. *Am. J. Psychiat.* 108: 703, 1952.

A dietary regimen is described for reducing the incidence of early secondary as well as eliminating

late secondary insulin reactions after the termination of insulin coma treatment. The authors believe that the administration of a combination of ice cream with Meritene® (whole protein diet supplement) instead of additional glucose after arousal from insulin coma is the chief factor in the elimination of nausea and vomiting and the reduction of the incidence of early secondary reactions. A high caloric afternoon meal and a meat sandwich in the evening reduce late secondary reactions.—I. A. MIRSKY

In experimental diabetes, the diet fed to the animal prior to the administration of alloxan or contra-insulin factors is of major importance, high protein diets in general affording the greatest protection.

Influence of Diet on the Incidence of Alloxan Diabetes. R. R. Rodrigues and W. A. Krehl. *Am. J. Physiol.* 169: 295, 1952.

The authors studied the toxic and diabetogenic effects of alloxan in rats fed various isocaloric diets over a period of one month. High and low protein diets were compared to high carbohydrate intakes. Diets high in protein reduced while low protein intakes increased mortality and the incidence of diabetes. There was a low incidence of diabetes when short-chain fatty acids made up most of the lipid. When lard was used, which was made up mostly of long-chain fatty acid, the toxicity and diabetogenic activity of alloxan was increased. Rats on high palmitic acid diets developed an increase in size of the Islets of Langerhans and a low incidence of diabetes. Emphasis is placed upon the different oxidation products of short- and long-chain fatty acids. This may serve as an explanation of their different actions.—M. J. OPPENHEIMER

Protein feeding in human diabetes has been shown to have little effect upon the blood sugar.

Protein Feeding and Blood Sugar Levels in Diabetes. E. R. Gubbay. *Canad. Med. Assoc. J.* 64: 150, 1951.

The addition of protein in the form of meat or casein to the diets of diabetic patients did not promote hyperglycemia. In one instance, the slow conversion of protein to carbohydrate may have been a factor in preventing insulin-induced hypoglycemia occurring with the use of protamine zinc insulin. Apparently liberal protein diets do not affect the normal blood sugar control.—C. R. SHUMAN

An interesting report follows on a patient receiving a high fat diet in the treatment of diabetes over a prolonged period of time.

A Diabetic Patient on a High Fat Diet for 29 Years without Complications. W. H. Johnson and E. H. Rynearson. *Proc. of the Staff Meetings of the Mayo Clinic.* 26: 329, 1951.

The patient described in this report developed diabetes in 1921, at which time the dietary treatment of diabetes involved the use of diets extremely low in carbohydrate content. He was standardized on a diet containing carbohydrate 15 Gm., fat 150 Gm. and protein 45 Gm. One year later, he was given insulin therapy and the diet was increased to 2750 calories of which 83 per cent was supplied as fat. In 1946, the insulin preparation was changed from regular to protamine zinc insulin.

In 1950, the patient was carefully restudied, at which time there was no evidence of vascular disease beyond that which would be anticipated at his age. The low carbohydrate content of the diet may account for the absence of signs of vitamin deficiency. Although this is only one case, and it would be difficult to induce others to follow such a diet for 29 years, it raises the question of the importance of a high fat intake in the production of degenerative vascular disease.—C. R. SHUMAN

Recently the use of fructose in intravenous feeding solutions has been subjected to study because of the possibility of avoiding hyperglycemia through its rapid entrance into the glycolytic cycle.

Metabolism of Intravenous Fructose and Glucose in Normal and Diabetic Subjects. M. Miller, W. R. Crucker, J. E. Owens, J. W. Craig, and H. Woodward, Jr. *J. Clin. Investig.* 31: 115, 1952

Fructose disappears more rapidly from the blood during intravenous infusion than glucose There is also a greater rise in blood pyruvate and citric acid. The metabolic responses to fructose were found to be normal in 5 diabetics in the absence of insulin. This is consistent with the observation that the phosphorylation of fructose is not influenced by insulin and hence proceeds at a normal rate. On the other hand, the phosphorylation of glucose to glucose-6-phosphate is impaired in the absence of insulin. A fall in serum inorganic phosphorus, which implies phosphorylation and utilization of the carbohydrate, was noted after fructose but not glucose in diabetes. —S. O. WAIFE

The Metabolism of Fructose as Related to the Utilization of Amino Acids when Both Are Given by Intravenous Infusion. R. Elman, M. D. Pareira, E. J. Conrad, T. E. Weichselbaum, J. A. Moncrief, and C. Wren. *Ann. Surg.* 136: 635, 1952.

Fructose is a better glycogen former than glucose, but has a low renal threshold. Few studies on fructose metabolism in man have been reported. Albanese recently found a better nitrogen balance when fructose rather than glucose was used in the diets of children. Elman and co-workers studied the nitrogen balance in 10 malnourished convalescent patients. On a completely intravenous subcaloric intake fructose improved nitrogen balance better than glucose or invert sugar. The more rapid entrance of fructose into cells makes it a better amino acid sparer than glucose.—S. O. WAIFE

Attempts to evaluate the type of diabetes or sensitivity to insulin have frequently been reported. A satisfactory test of this sort may prove useful in outlining treatment programs for diabetic patients.

The Estimation of Insulin Sensitivity by the Modified Glucose Insulin Tolerance Test. S. S. Lazarus and B. W. Volk. *J. Lab. and Clin. Med.* 39: 404, 1952.

One-tenth of a unit of crystalline insulin per kilogram of body weight was injected intravenously thirty minutes after the intravenous administration of 50 cc. of 50 per cent glucose. Capillary blood was analyzed for glucose, by Nelson's modification of Folin-Wu method, in 40 fasting non-diabetic controls as well as in 24 fasting diabetics who had had no insulin for 48 hours. The latter group consisted largely of aged patients with variegated complications and insulin requirements ranging from 0 to 95 units a day. The blood sugar fell to the fasting value within forty-five minutes after insulin injection in all control subjects and in only 7 diabetics was this fall thought to be significantly delayed. Analogous findings were obtained with respect to rate of fall of blood sugar during thirty minutes after insulin administration. The authors tend to interpret their findings to indicate the existence of discrete insulin-sensitive and resistant groups of diabetics. In the opinion of the present reviewer, however, neither criterion of insulin resistance, i.e. delay in return to fasting concentration of blood sugar or slow rate of fall of blood sugar, provides cogent evidence for a rigorous or clear-cut separation with respect to sensitivity or resistance to insulin. Interestingly enough, there was, in some diabetics, a greater acceleration in rate of fall of blood sugar during the combined glucose-insulin procedure beyond that observed after glucose administration alone, as compared to controls. This evidence of abnormally *increased* sensitivity to insulin in diabetics may have been mediated in part by the mass action effect of higher concentrations of blood sugar.—R. TARAIL

The concentration of hepatic glycogen in uncontrolled diabetes mellitus has usually been regarded as being reduced. Studies of human diabetics have not confirmed this finding previously made in animals.

Liver Glycogen in Diabetes Mellitus. J. Vallence-Owen. *J. Clin. Path.* 5: 42, 1952.

The livers of 31 diabetic patients dying of diabetic coma and 25 control subjects dying of other conditions were examined for cytoplasmic glycogen content. Six of the 15 diabetics who had received no insulin were found to have reduced amounts of glycogen in the liver, while the remainder showed normal or increased amounts of glycogen. All of the diabetics who had received insulin had normal hepatic glycogen distribution. The control subjects dying of debilitating illnesses showed less glycogen than the untreated diabetic coma patients. The author suggests that the overproduction theory of diabetes may explain the finding of glycogen-loaded livers in the presence of ketosis.—C. R. SHUMAN

The use of the hyperglycemic factor from the pancreas may provide information relative to the hepatic glycogen content.

Effects of Pancreatic Hyperglycemic Factor on Hepatic Carbohydrate Metabolism of Man. J. D. Myers, R. F. Kibler, and W. J. Taylor. *Fed. Proc.* 11: 111, 1952.

Pancreatic hyperglycemic factor (HGF) promotes a rapid and substantial rise in blood glucose in man by augmenting splanchnic glucose production. There is usually a strikingly subnormal hyperglycemic response in diffuse liver disease (cirrhosis, hepatitis), suggesting that HGF may provide a simple test for hepatic glycogen content.—S. O. WAIFE

Protein-bound iodine levels in diabetic children have been found to be reduced in early adolescence. However, in older children, the levels are normal.

Protein-Bound Iodine Levels in Normal and in Diabetic Children. T. S. Danowski, S. J. Huff, L. H. Erhard, M. Price, M. Brown, P. Wirth, and S. S. Stevenson. *Am. J. Dis. Child.* 84: 5, 1952

The authors have applied their new semi-micro-analytic procedures for the determination of protein-bound iodine to normal children to ascertain its reliability as a measure of thyroid function. In addition, a series of children with diabetes mellitus have been studied. This effort is prompted by the well-known defects in utilizing basal metabolism rate and other methods as indices of thyroid function. In a group of 64 apparently normal children from 6 to 18 years of age, the level of protein-bound iodine averaged 4.7 $\pm$ 0.8 μg. per ml. This paper is not concerned with data from children with thyroid disease and does not endeavor to establish the use of protein-bound iodine as of superior value in the diagnosis of thyroid function in children. Reference is made to previous publications in which this question is considered in adults. In the children under treatment for diabetes mellitus the mean value for protein-bound iodine was not statistically different from the normal group. The implications of a trend toward lower levels of protein-bound iodine in the early adolescent years of diabetic children are briefly discussed.—C. D. MAY

Little is known of the effect produced by the administration of various drugs upon diabetes mellitus. The following paper presents evidence indicating that "amithiazone" given to tuberculous diabetic patients is associated with further impairment of carbohydrate tolerance.

Disturbance in Carbohydrate Metabolism Associated with Amithiazone Therapy. W. E. Escovitz. *Am. Rev. Tuberc.* 66: 373, 1952.

The author reports two cases of pulmonary tuberculosis in which impairment of carbohydrate metabolism was associated with the prolonged administration of amithiazone. In one patient diabetes apparently developed *de novo,* whereas the other patient had diabetes before amithiazone therapy was started and the diabetes was aggravated by the treatment. In both cases the diabetes was well controlled on cessation of amithiazone, became worse when the drug was given again, and again became well controlled when the drug was stopped. That the glycosuria and hyperglycemia were due to glucose was proven by fermentation studies of blood and urine. One patient had evidence of impaired renal and liver function before amithiazone was started, while the other patient was normal. Uric acid, 17-ketosteroid, and uropepsin excretion studies were not changed in either case during amithiazone therapy. The author concludes that the mechanism of carbohydrate metabolism impairment during the administration of this drug in these two cases is not known. Few such cases have been previously reported.—W. Weiss

FLUORINE AND WATER

Addition of fluoride to water supplies for the prevention of dental caries has been a subject of study for several decades. The suggestion that fluoride was important in this connection arose from observations that the incidence of carious teeth was lower than average in areas having increased concentrations of fluoride salts in the drinking water. The initial article summarizes current thoughts on the ingestion of fluoride for the control of dental caries.

Choice of Fluoridating Agents in the Control of Dental Caries. C. L. Howell, L. E. Burney, Harry G. Day, and Joseph C. Muhler. *Amer. J. Public Health* 42: 44, 1952

It is stated that the continuous ingestion of a communal water supply of sodium fluoride at a level of one part per million reduces the incidence of dental decay by 60 to 65 per cent if consumed from birth onward. The same results applied for naturally occurring fluorine in communal water supplies in a study of children 7 to 17 years of age. On the other hand, the topical application of 2 per cent sodium fluoride in 7- to 17-year-old children limits the incidence of dental caries only to 40 per cent. It is considered that the compound of choice is sodium fluoride for the purpose of artificially influencing communal water supplies. Although study of the long-term effects of supplementary fluorine ingestion is incomplete, it is apparent that we have reached the stage of considering fluorine as a sort of "accessory food factor" for its effect in diminishing dental caries.—A. J. Steigman

The Connections between Dental Caries Experience and Water-borne Fluorides in a Population with Low Caries Incidence. P. Adler (with I. Sárkány, K. Tóth, J. Straub, and E. Szeverényi). *J. Dent. Res.* 30: 368, 1951.

In Hungary, where caries susceptibility and incidence are low, optimum concentrations of fluorides in the drinking water caused inhibition rather than delay in the first molar caries experience of school children aged 9 to 11 years. Fluorinated water is effective in the protection against caries only if used during the first 6 years of life.—*Nutrition Abstracts and Reviews* 21: 739, 1952.

The following observations on the action of the placenta are of significance in relation to the fluoridation of water supplies.

The Fluoride Content of Placental Tissue as Related to the Fluoride Content of Drinking Water. B. E. Gardner, F. A. Smith, H. C. Hodge, D. E. Overton, and R. Feltman. *Science* 115: 208 1952.

A study of placental tissue which came from patients in Rochester and Newburgh, New York, revealed that the increased level of fluoride in the water of Newburgh resulted in a higher concentration of fluoride in the placental tissue, which may be related to the blood fluoride concentration. From both communities the placental samples had higher concentrations of fluoride than the blood samples. This may be due to the fact that if fluoride is an essential trace element, the placenta may act as a concentrating organ to insure that the fetus will have adequate fluoride for developing tissue; or secondly, since excessive fluoride is toxic, the placenta may act as a barrier to prevent more than trace amounts of fluoride from reaching the fetus.—S. O. Waife

General adoption of the policy of adding optimal concentrations of fluorine to community drinking water seems likely.

Report on Fluoridation of Water Supplies. Committee on Public Health Relations of the New York Academy of Medicine. *Bull. of the New York Acad. of Med.* 28: 275, 1952.

Having weighed the advantages and disadvantages in the light of expert opinion, the Committee recommends that New York City be urged to proceed with the fluoridation of the public water supply as a measure for the prevention of dental caries.

Since fluoridation is not a cure for all dental ills, the Committee recommends that the dental health education and service program, including topical application, now carried on by the Bureau of Dentistry in the Health Department, be continued for the care of those who have not had the benefit of this preventive measure in their early years.

An educational program to promote general acceptance of the program in the community is recom-

mended to the Department of Health.—C. F. WILKINSON, JR.

However, in view of the following unfavorable report, it is apparent that further observations on the results obtained using fluoridation as a preventive measure for control of caries are necessary.

Unfavorable Report from Kansas Community Using Artificial Fluoridation of City Water Supply for Three-Year Period. C. A. Scrivener. *J. Dent. Res.* 30: 465, 1952.

Ottawa, Kansas, was selected by the State Board of Health as the site of a 10-year pilot study on fluoridation and caries incidence. Careful dental examinations of some 100 children, aged 5–6, made at the beginning of the trial period (1946), showed 82.3 per cent caries-free children. Three years later, approximately 100 children in the same age group were examined; only 45.0 per cent were found to be caries-free.

The test will continue to run its 10-year course, and no explanation is offered of this exception to the usually favorable results from fluoridation of community water supplies.—C.-J. HOWELL

VITAMIN-HORMONE INTERRELATIONSHIPS

Ascorbic Acid and Adrenal Function

Isotopic studies have shown that cholesterol, found in the adrenal gland in high concentration, is a precursor of adrenocortical hormones. Ascorbic acid, which is also present in the adrenal is in some way related to adrenal cortical function. This interrelationship is poorly understood at present but current research has begun to shed some light on these matters which will have significant clinical implications.

Several reports have shown that the adrenal may function normally in the presence of severe vitamin C deficiency.

Ascorbic Acid Requirements in "Damage" and its Relationship to Adrenocortical Activity. R. M. Kark, R. E. Chapman, and C. F. Consolazio. *Proc. Am. Soc. Clin. Investig.* 44th meeting, Atlantic City, 1952.

Studies in man, utilizing data derived from plasma, whole blood, fecal and urinary ascorbic acid, circulating eosinophils, and urinary 17- ketosteroid excretion, reveal that in classical scurvy there was a good adrenocortical response to ACTH, as evidenced by a fall in eosinophils and a rise in ketosteroid excretion. There was no change in blood, urine, or fecal ascorbic acid levels. Indeed, no change in these levels was noted following ACTH or cortisone therapy in individuals "saturated" with ascorbic acid. On the other hand, a considerable diuresis of ascorbic acid occurred in the "saturated" group, perhaps comparable to adrenocortical glycosuria.—S. O. WAIFE

Response to Adrenocorticotrophic Hormone in Clinical Scurvy. H. S. Treager, G. J. Gabuzda, N Aamcheck, and C. S. Davidson. *Proc. Soc. Exp. Biol. Med.* 75: 517, 1950.

The effect of ACTH on blood eosinophils and urinary uric acid was studied in 5 patients with clinical and laboratory evidence of scurvy. All subjects had perifollicular hemorrhages, ecchymoses, a positive tourniquet test, and a low ascorbic acid content in the buffy coat of packed blood cells. The dietary histories were in keeping with vitamin C deficiency.

The response to ACTH was normal and was not affected by repletion of ascorbic acid. The authors concluded that either ascorbic acid is not essential for these adrenal functions, or that residual adrenal ascorbic acid was present.—S. O. WAIFE

On the other hand, it is possible that prolonged adrenal stimulation (such as corticotropin [ACTH] administration) may deplete the adrenal and the body of ascorbic acid.

Manifestations of Ascorbic Acid Deficiency after Prolonged Corticotropin Administration. H. L. Holley and J. S. McLester. *Arch Int. Med.* 88: 760, 1951.

Two cases are presented which seem to reinforce experimental evidence that prolonged administration of corticotropin (ACTH) may lead to ascorbic acid deficiency. Two patients with rheumatoid arthritis had been treated over long periods with corticotropin. Signs of scurvy appeared after 6 months in one case, and after nearly a year in the other. In both instances the hemorrhagic manifestations receded dramatically when massive doses of ascorbic acid were given, and liberal supplements of this vitamin prevented their reappearance during successive corticotropin therapy.

While this hemorrhagic tendency does not often occur during corticotropin therapy, the authors believe that the possibility of ascorbic acid deficiency should be considered whenever the prolonged administration of this hormone is accompanied by signs suggestive of scurvy.—C.-J. HOWELL

There is histologic evidence of ascorbic acid-adrenal interrelations. Morphologic changes in the adrenal may be produced experimentally with diets deficient in ascorbic acid.

Ascorbic Acid Intake and the Adrenal Cortex. R. Stepto, C. L. Pirani, C. F. Consolazio, and J. H. Bell. *Endocrinology.* 49: 755, 1951.

Reduction of ascorbic acid intake in the male guinea pig was associated with the following changes: (1) adrenal cortical hypertrophy, (2) reduced adrenal ascorbic acid and cholesterol ester content, (3) preservation of the zona glomerulosa, thickening, some cellular disorganization, loss of sudanophilic material, and reduced birefringency of the zona fasciculata, (4) a reduction of liver glycogen, (5) no important changes in the thymus or lymph nodes, (6) normal

serum sodium, and a probably insignificant rise in blood sugar.

It was therefore concluded that severe ascorbic acid deficiency caused a reduction of steroid concentration in the adrenal cortex. The authors hypothesized that this could be due to either a stress induced steroid depletion and adrenal cortical exhaustion or a diminished corticosteroid synthesis in the absence of an adequate concentration of ascorbic acid.—N. G. SCHNEEBERG

Since ascorbic acid has been considered by some workers as an index of tissue cell activity, a study was made of the ascorbic acid content of various cells of the pituitary gland in order to localize the site of production of corticotropin.

Ascorbic Acid Content of the Pituitary after Adrenalectomy. Histochemical Study. R. E. Mancini and C. Dosne de Pasqualini. *Compte. rend. Soc. de biol.* 145: 585, 1951.

In an effort to pinpoint the pituitary cell responsible for the secretion of corticotropin—known to increase upon disappearance of the circulating cortical hormones—the authors studied the localization of ascorbic acid in the pituitary cells of totally and unilaterally adrenalectomized rats. Total adrenalectomy led to the accumulation of ascorbic acid in the acidophile cells. Unilateral adrenalectomy or the administration of desoxycorticosterone acetate (DCA) prevented these changes. These results are interpreted as indicating that the acidophile cells of the pituitary are responsible for the production of corticotropin.—S. O. WAIFE

It is significant to note that plasma ascorbic acid levels do not reflect the nutritional state with respect to this vitamin. The plasma level is affected by many factors including the state of endocrine activity.

Plasma Ascorbic Acid and Pituitary-Adrenal Activity. F. R. Skelton and C. Fortier. *Canad. J. Med. Sci.* 29: 176, 1951.

There is a fall in plasma ascorbic acid level about 30 minutes after trauma, exposure to cold, etc., followed by a rise to above normal and gradual decline to normal levels. Adrenalectomy alone led to a fall in ascorbic acid levels, but the plasma level in response to stress resembled that of the intact animal. Similar responses were noted in hypohysectomized animals.

Administration of lipo-adrenal extract after adrenalectomy led to a rapid, marked, although temporary, rise in plasma ascorbic acid.—S. O. WAIFE

The question as to whether ascorbic acid should be administered in large doses in patients undergoing "stress" reactions cannot be answered at this time. The possibility of a synergistic action between the vitamin and the adrenal cortical hormones is noted and a possible mode of interaction is described in the following paper.

Prolongation of Effects of Adrenal Cortical Secretion by Ascorbic Acid: Proposed Mechanism of Action. H. Bacchus, N. Altszuler, and M. H. Heiffer. *Proc. Soc. Exp. Biol. Med.* 80: 88, 1952.

That ascorbic acid prevents the alarm reaction to acute stress, whether induced by trauma or epinephrine, has been demonstrated in experimental animals. The fact has been interpreted to mean that the action of ascorbic acid is, in these conditions, similar to that of cortical hormones. However, other experimental data indicate that ascorbic acid does not produce its anti-stress effect alone, but synergistically with cortical hormones.

In the experiments reported here, it was found that the leukocytic effects of cortisone injections, as of ACTH-induced secretion of endogenous cortical hormones, are prolonged by ascorbic acid. In adrenalectomized rats, the eosinopenic and lymphopenic effects of cortisone persisted longer in those treated with ascorbic acid than in controls. Since ascorbic acid *per se* does not effect leukocyte pattern, this is explained as a synergism between cortisone and ascorbic acid. In adrenal-demedullated rats injected with ACTH, the hematologic effects of the hormone were prolonged in animals receiving simultaneous ascorbic acid.

Relating these data to other experimental observations, the authors postulate that ascorbic acid blocks the activation of the pituitary-adrenal axis by non-specific stressors, though the precise level at which this interference takes place is not yet clear. The suggestion is offered that ascorbic acid may somehow inhibit the activation of the pituitary. If the level of circulating cortical steroids regulates pituitary-adrenotropic activity (high titers depressing ACTH release by the pituitary), and if ascorbic acid decreases the inactivation of cortical hormones, its administration might, by maintaining higher circulating cortical hormone levels, prevent activation of the axis by non-specific stressors. However, the authors do not imply that ascorbic acid is necessary for the secretory activity of the adrenal, pointing out that ACTH provokes adrenal production of cortical hormones even in scorbutic animals.—C.-J. HOWELL

ITEMS OF GENERAL INTEREST

Present Status of Deficiency States. C. J. Barborka. *Canad. M. A. J.* 66: 105, 1952.

In this article the author points out that the occurrence of deficiency diseases in the United States has not been noted generally. On the other hand, every national survey in the past decade has revealed that the consumption of diets which are below recommended standards is widespread throughout the United States. The remainder of the article is an attempt to reconcile these two statements and to out-

line a technique for the detection of early or "subclinical" nutritional deficiencies.

The author rightly points out that while in the laboratory most nutritional deficiencies are created singly, seldom does one see this in clinical medicine. The clinical picture is rather one of multiple mild deficiencies rather than a single predominant one. Many of the symptoms that are commonly referred to as neurotic in nature can be shown to be due to such multiple mild deficiencies. Common among the symptoms of early deficiency states are the following: poor appetite, lost weight, lost strength, weakness, indigestion and dyspepsia (heartburn), diarrhea, constipation and abdominal cramps, vague burning, itching, crawling sensations over the skin, nervous, irritable and depressed reactions with inability to sleep, apprehension, weeping spells, forgetfulness, and mental confusion.

The technique for the diagnosis of deficiency states is divided into five steps: (1) A careful scrutiny of the diet (food eaten), even to the extent of having the patient keep a diet for a week or ten days. (2) To be alert for signs and symptoms of a deficiency as determined by history and physical examination. (Here the author goes into all of the various physical manifestations of deficiency state as well as the symptomatic ones referred to above.) (3) To investigate factors which influence the digestion, the absorption, and the utilization of the diet. (This is particularly important now with the new antibiotics which may change the intestinal flora or with individuals who have had mechanical alterations of their intestinal tract rendering them deficient even though they are on an adequate diet.) (4) To make laboratory tests by the methods described for the presence of various vitamin deficiencies. (This may be somewhat more difficult in the usual hospital laboratory than the author implies.) (5) Therapeutic trial with specific vitamin concentrates. (Here he recommends combinations of vitamins, etc., with a warning of overdosage, not so much because of danger as the harm it will do to a patient's pocketbook.)

This appears to be an excellent article and his technique for determining deficiency state is good. The only real criticism appears to be that while in his introduction he makes his point that deficiency states are multiple and mild, he ends up recommending that they be treated by single vitamins or combinations of single vitamins. This seems indefensible to the reviewer, and a plea should be made for the use of naturally occurring combinations of vitamins such as Brewer's yeast, wheat germ, and particularly foods which are rich in the material in which the patient is suspected of being deficient.—C. F. Wilkinson, Jr.

Reliability of the Clinical Assessment of "Nutritional State." E. R. Bransby and W. H. Hammond. *Brit. Med. J.* 2: 330, 1951.

The nutritional state of two groups of children was assessed in two British communities. The evaluation included an examination of the general physical status and a search for certain clinical signs. The clinical signs enumerated were pallor, fatigue, lethargy, poor posture, diminished fat, poor muscle tone and development, and inelastic skin; as the incidence of these signs increased, the nutritional grading diminished. There was found to be little agreement among the clinicians as to the grading of the nutritional status or the incidence of clinical signs. When the same examiner was confronted later with a group of children previously examined by him, there was disagreement in the findings of the two examinations.

There was close agreement between the clinical grade and the incidence of certain clinical signs. Thus the clinicians involved were able to associate the clinical signs with nutritional grades. Therefore, if the clinical signs could be made more objective, a more satisfactory system of grading could be evolved. —C. R. Shuman

The Evaluation of Leanness-Fatness in Man: Norms and Interrelationships. J. Brožek and A. Keys. *Brit. J. Nutr.* 5: 194, 1951.

This communication is part of a long-range investigation on the effects of aging, with emphasis on the cardiovascular system. However, this paper deals only with fat content of normal men free from disease.

Body fat shows the most striking variations in states of nutrition, varying from emaciation to obesity. The quantitative estimation of the relative fatness of the human body is essential for the establishment of valid estimates of caloric requirements. The characterization of man's "leanness-fatness" in this paper is based on the measurement of (1) specific gravity of the body, (2) thickness of skinfolds, and (3) external dimensions and body weight. In living man the percentage of the body fat, estimated on the basis of specific gravity of the body, seems to be the best single criterion for measuring the individual's leanness-fatness. The skinfolds are regarded as the second best index. "Impure" characteristics, such as the abdominal circumference and the gross body weight, furnish still more indirect yardsticks of the leanness-fatness of an individual.

In selecting the subjects, several criteria were applied: (1) health—subjects had to be free of discoverable disease; (2) sex—only men were included; (3) age—two groups were selected, 133 young men of college age, with an average of 20.3 years, and 122 older adults with an average of 49 years; (4), occupation—the younger men were students at the University of Minnesota, the older men were business and professional men in Minneapolis and St. Paul; (5), relative weight—a fairly wide range was desired.

Equations for prediction of specific gravity(and the corresponding percentage of body fat) from single and combined criteria of fatness were developed.

The data submitted may provide useful reference material for other investigators. Extension of this work to other age levels and to women is needed.—B. SURE

Comparative Effects of a Purified and an Adequate Diet on the Course of Fatty Cirrhosis in the Alcoholic. G. B. Phillips, G. J. Gabuzda, Jr., and C. S. Davidson. *J. Clin. Invest.* 33: 351, 1952.

Three alcoholics with large, fatty livers were studied from the standpoint of liver size, function, and histology during a period of 8–13 days on a highly purified diet consisting of sugar water and salt and during a subsequent period on an "adequate" diet which was the normal house diet. During the initial regimen liver size did not change; liver function tests for the most part worsened; liver histology, especially fat, did not change appreciably. However after 7–8 days on the "adequate" diet definite improvement in liver function occurred in all three patients. The liver decreased in size in one patient. An observable decrease in the amount of fat occurred within 8–14 days in all patients.

The oft observed clinical association of alcoholism and cirrhosis of the liver is as yet not clearly defined. Whether the cirrhosis is a result of the hepatotoxic effect of alcohol *per se* or the nutritional deficiency secondary to the alcoholism, or to a combination of these factors, remains unanswered. This experiment was an attempt to define more clearly these factors. Unfortunately, the use of such a severely restricted diet in which the daily caloric intake was 1600 or less introduces another factor. The results here suggest that abstinence from alcohol and bed rest alone are ineffective in promoting liver healing, but that food is necessary. However this experiment in no way sheds light upon the causation of the liver damage, for one would expect foodstuff to help regardless of the causation, whether it be virus, heavy metal, alcohol, or nutritional deficiency.—J. F. MUELLER

Riboflavin Excretion as a Function of Protein Metabolism in the Normal, Catabolic, and Diabetic Human Being. H. Pollack and J. J. Bookman. *J. Lab. Clin. Med.* 38: 561, 1951.

This is an interesting and important report. It was found that nutritionally normal subjects usually retain over 50 per cent of ingested riboflavin when in nitrogen equilibrium, and less than 50 per cent when in negative N balance.

During catabolic states, such as follow surgical procedures, there is a marked excretion of riboflavin; conversely, in convalescence, riboflavin retention seems to follow protein formation, assumed from positive N balances.

Similar patterns were observed in diabetics in whom negative N balances were induced by reduction in insulin administration or caloric restriction.

In the discussion the authors present their concepts of a nitrogen metabolic pool and labile reserves of protein, to which the interested reader is referred.

Assaying the nutritional status of riboflavin of an individual by means of urinary excretions or load tests would seem to be questionable, since the result would hinge on current or immediately past N balance. On the other hand, the importance of an adequate vitamin intake to a diabetic is clear.—S. O. WAIFE

Blood Glucose and Food Intake in Normal and Hypophysectomized, Alloxan Treated Rats. J. Mayer, and M. W. Bates. *Am. J. Physiol.* 168: 812, 1952.

When hyperglycemia of short duration was produced in normal rats by injections of glucose and adrenalin there was a decrease in food intake. Insulin-induced hypoglycemia was accompanied by increased food intake although the depression of blood sugar was only equal to that seen in fasting. Injections of control substances which did not influence blood glucose levels were without effect. Prolonged hyperglycemia had an even greater effect in decreasing food intake in hypophysectomized, alloxan-treated animals. These last-mentioned animals were unable to regulate blood sugar levels.

The authors suggest a "glucostatic mechanism" which would regulate the intake of food. According to this proposal the blood sugar is the normal stimulus for hypothalamus or other receptors. Impulses from the hypothalamus by way of cortical connections plus sensory impressions from the stomach could bring about the search for food and regulate the amount taken. This is an interesting suggestion, since nervous tissue requires glucose in its metabolism. The role of glucose is not conceived as that of a chemical messenger in this glucostatic mechanism but rather as an essential metabolite of nervous tissue. Glucose would be important to the hypothalamus as a large source of high energy phosphate bonds. The hyperphagia of diabetes in this schema may be due to functional starvation of hypothalamic centers despite the hyperglycemia. These regulating centers cannot utilize glucose and are hence partly starved for glucose which they need for metabolism. They are thus deprived of high energy phosphate sources. Hyperphagia and further hyperglycemia result. This hyperphagia and subsequent hyperglycemia are defense mechanisms set into motion by the "starvation" of the regulating centers.—M. J. OPPENHEIMER

This provocative paper suggests that the level of blood glucose may be one of the factors controlling appetite. The response of the hypothalamic centers to blood glucose may regulate food intake. A similar "satiety" center operating through a different mechanism to control food intake has been demonstrated by Brobeck.

The Composition of Human Milk with Special Reference to the Relation between Phosphorus Partition and Phosphatase and to the Partition of Certain Vitamins. R. Chanda and E. C. Owen. *Brit. J. Nutr.* 5: 228, 1951.

This work was undertaken to determine if the changes in human milk at the beginning of lactation were at all comparable with those in cow's milk immediately after parturition.

No milk was collected in the summer months to prevent the risk of possible changes in transit. Analyses were completed within 48 hours of arrival of the samples at the laboratory. The total number of samples collected was 52, but analyses for all the constituents studied could not be made on all of them.

Phosphoric acid was determined with the aid of an absorptiometer. Fats, solids not-fat, protein, and phosphatase were analyzed by standard methods. Thiamine was estimated in skimmed milk after treatment with takadiastase. Nicotinic acid was estimated microbiologically. In estimating carotenoids and vitamin A, it was found that besides beta-carotene and xanthophyll, human milk fat contained appreciable amounts of alpha-carotene and lycopene. These substances were separated chromatographically.

Samples of normal milk from mothers delivered in the Aberdeen Maternity Hospital were collected at intervals up to 28 days after parturition, and were analyzed for various constituents, with the following results:

The percentage of protein was only 0.63, on the second day *post partum*, but rose to 2.01 the next day and remained at about that concentration thereafter. The percentage of fat ranged from 2.5 to 3.9. The percentage of solids not-fat varied from 9 to 10, with an initial figure of about 11.2. The amounts of inorganic, ester, and lipid phosphorus were closely correlated with the phosphatase content of the milk—that of inorganic phosphorus positively, and that of ester and lipid phosphorus negatively. The amount of phosphatase in the milk was large at first, falling as lactation progressed. The N: P ratio was 20 in human milk, compared with only 6 in cow's milk.

The amount of nicotinic acid increased from 42 μg./100 ml. on the third day *post partum* to 226 μg./100 ml. on the twenty-eighth day. The amount of total thiamine increased steadily with the advance of lactation, becoming steady on the eighth day.

The claim by the authors that the thiamine content of human milk is readily affected by dietary intake needs some comment. Morgan and Hayes (*J. Nutr.* 18: 105, 1939) of the United States concluded from their study that the level of thiamine in human milk is controlled only in the lower brackets by the vitamin B_1 content of the diet, but, as in cow's milk, a maximum level exists above which the vitamin B_1 content cannot be raised even by massive doses of thiamine chloride.

The vitamin A activity of the milk was mainly due to vitamin A itself. The contribution from carotenes was very small. Of the vitamin A, more than 90 per cent was in the ester form. Two-thirds to four-fifths of the activity of the carotenes was due to beta-carotene and the remainder to alpha-carotene. Lycopene, which is not a carotenoid, formed one-quarter to one-half of the total carotenoids. The vitamin A concentration in the milk fat was larger at first than in later lactation.—B. SURE

Vitamin A Levels in Health and Disease. T. Moore and I. M. Sharman. *Brit. J. Nutr.* 5: 119, 1951.

The levels of vitamin A in the blood plasma and tissues are influenced by numerous factors, such as rate of intake, efficiency of absorption, storage in the liver and other tissues, its mobilization from the liver into the blood plasma, and its removal from the plasma by transfer to the tissues, by destruction, and by urinary excretion.

The levels of vitamin A and carotenoids in the plasma of inhabitants of Great Britain and the United States are presented. The results are expressed as International Units (I. U.) per 100 ml. of plasma. Among 305 subjects in Great Britain the carotenoids ranged from 133 to 150 and vitamin A from 108 to 120. In the United States among 213 subjects the carotenoids concentrations varied from 294 to 343 and vitamin A from 104 to 160.

The effect of giving massive doses of vitamin A in raising its level in the plasma has been studied. In normal subjects a sharp rise is observed 4 to 5 hours after dosing, followed by a return to the resting level in 24 hours. "Tolerance" curves can be thus obtained. Flattened curves were observed in sprue, celiac disease, and infective hepatitis, in which the absorption of fat is affected. Greatly elevated curves have been found in children with nephrosis, in whom the power of the liver to absorb or to utilize vitamin A has been seriously impaired. In conditions of impaired fat absorption, vitamin A was much more efficiently absorbed from aqueous emulsions than from oils.

Data have been presented on vitamin A reserves found in groups of human subjects who died by accident within 7 days of injury or from various diseases. Vitamin A reserves (expressed as I. U./Gm. liver above the levels of those dying from accidents) of 220 I. U./Gm. were found in diabetes (300) and thyroid diseases (310). Reserves were more severely reduced in some diseases than in others. Infections of the head and spine gave a median of 73 I. U./Gm. liver and abscesses in other sites gave one of 51. For pneumonia the median was 63, and for empyema, 60. The lowest values were found for urinary diseases, with 25 for chronic nephritis, and 19 for urinary infections.

Normally, vitamin A, being soluble only in fat, is not excreted in urine. However, patients with certain diseases, including pneumonia, chronic nephritis, and

icterus with closure of the biliary duct, passed considerable amounts of vitamin A into their urine.—B. SURE

Pathology of Vitamin A Deficiency and Its Clinical Symptoms. Z. A. Leitner. *Brit. J. Nutr.* 5: 130, 1951.

Vitamin A deficiency produces metaplasia in tissues, resulting in keratinized epithelium. Mainly affected are epithelia with secretory function, such as the salivary glands, including the tongue and pharynx, the respiratory tract with trachea and bronchi, the eyes, including the cornea and conjunctiva, the genitourinary tract, with the renal pelvis, ureter, and bladder, and the sex glands. In man, the skin may also be involved. On the other hand, the liver does not show much atrophy or keratinizing metaplasia.

The nerve lesions, due to vitamin A deprivation, demonstrated in animals to be caused by bone pressure, have not yet been recognized as an effect of this vitamin deficiency in man. The clinical significance of vitamin A deficiency has been referred to in relation to hemeralopia, Biot's spots, xerophthalmia, and keratomalacia and has been discussed at greater length in relation to certain skin diseases (Darier's disease, and pityliasis rubra pilaris), to involvement of the liver, and to febrile states. It has been suggested that it might prove advantageous to give 40,000 to 50,000 International Units Vitamin A daily in rheumatic fever, and in pregnancy complicated by febrile states, especially during the first trimester.

The possible relationship of vitamin A deficiency to two inherited diseases in man, fibro-cystic disease of the pancreas and pityriasis rubra pilaris, has been discussed.

It has been also suggested, based on results of animal experimentation, that the frequency of congenital malformation may be enhanced by vitamin A deficiency in the maternal diet during gestation, and, further, that neonatal mortality and the incidence of congenital malformation in man may increase under unfavorable nutritional conditions.—B. SURE

Effect of Individual Vitamins A, C, E, and Carotene Administered at High Levels on their Concentration in the Blood. C. Urbach, K. Hickman, and P. L. Harris. *Exper. Med. & Surg.* 10: 7, 1952.

Normal adult males received large oral supplements of a single vitamin in addition to an adequate diet. Vitamin A supplementation lasting for 21 weeks (in doses of over 46,000 units daily, about 10 times the usual recommended allowance) led to an increase in plasma vitamin A level of only 16 per cent above the control values. By the end of the supplementation period the plasma level had substantially returned to the pre-treatment level. Large doses of vitamin E (125 mg. of mixed tocopherols daily) and vitamin C (179 μg. daily for 12 weeks, then 91 μg. for 14 weeks) also led to a transient elevation in plasma level with a subsequent decrease to levels essentially indistinguishable from unsupplemented controls.

The response to carotene was different in that storage and regulatory mechanisms did not prevent the rise in blood carotene concentration to high levels.

Minor infections, deep emotional disturbances, and exhaustive work led to temporary precipitous drops in ascorbic acid levels.

The authors rightly conclude that the plasma values of some vitamins in normal subjects are not necessarily an indication of "vitamin status" or of response to therapy, and short-term vitamin supplement experiments might produce misleading results.—S. O. WAIFE

A Study of Test Dose Excretion of Five B Complex Vitamins in Man. F. T. Lossy, G. A. Goldsmith, and H. P. Sarett. *J. Nutrition* 45: 213, 1951.

In this investigation an oral test dose of thiamine, riboflavin, and nicotinamide was administered to 115 individuals, including 39 normal persons and 76 in the clinics or wards of the Charity Hospital of Louisiana or in the Hutchinson Memorial Clinic of Tulane University. Excretion of the vitamins was studied in relation to clinical findings and to dietary histories. Pyridoxal and folic acid were included in the test dose later in the study, in order to determine whether there was any relationship between the level of excretion of these vitamins and nutritional status.

The following test dose procedure was adopted: a tablet containing approximately 5 mg. of thiamine hydrochloride, 5 mg. riboflavin, and 50 mg. nicotinamide, was given with two glasses of water about half an hour before breakfast. In the latter part of the investigation, 25 mg. of pyridoxal hydrochloride (dissolved in part of the water) and a 5-mg. tablet of folic acid were given at the same time. Urine was collected for a 4-hour period, acidified with about 3 ml. of glacial acetic acid, and kept in amber bottles in a refrigerator. The volumes of the 4-hour specimens and the creatinine excretion were used as indices of the completeness of urine collection.

The mean thiamine excretion after the test dose was found to be significantly lower in patients with thiamine deficiency and in subjects who had been maintained on weighed diets low in B vitamins. Riboflavin excretion was appreciably decreased only in the group of subjects on weighed diets low in B vitamins. The excretion of N′-methylnicotinamide was less than that of the control subjects in all groups tested. Folic acid was lower in subjects with evidence of thiamine or vitamin B complex deficiency than in control subjects. The excretion of 4-pyridoxic acid was essentially the same in all of the groups tested.

In subjects with diabetes mellitus, the mean excretion of thiamine and riboflavin was significantly higher than that found in control subjects, while that of N′-methylnicotinamide was lower.—B. SURE

Vitamin Studies in Middle-Aged and Old Individuals. VII. Roentgenological Studies of the Gastrointestinal Tract in Patients with Hypovitaminemia B_1. J. E. Kirk and M. Chieffi. *Gastroenterology* 20: 309, 1952.

Roentgenological examinations of the gastrointestinal tract were performed in 20 middle-aged and elderly individuals with blood thamine levels above 3.5 μg. per cent (3.5 to 6.0), and in 20 patients free of obvious gastrointestinal disease but with blood thiamine concentrations below 2.4 μg. per cent (0.0 to 2.4). The latter group was reëxamined 3 months later when the blood thiamine level had reached figures above 3.5 μg. per cent. No significant radiological abnormalities were observed in either of the groups examined. Clinical signs of edema of the legs, tenderness of the calves, and impairment of vibratory sense, noted alone or in various combinations in 17 of the 20 hypothiaminemic patients, disappeared after 3 months of daily administration of 5 mg. of thiamine hydrochloride.—J. E. BERK

Prevention of Certain B Vitamin Deficiencies with Ascorbic Acid or Antibiotics. F. S. Daft and K. Schwarz. *Fed. Proc.* 11: 200, 1952.

Large doses of ascorbic acid or aureomycin prevent or delay the signs of pantothenic acid and riboflavin deficiency in rats. Deficient rats died as expected, but litter-mates (on 2 per cent ascorbic acid or 20 mg. per cent aureomycin) on identical diets lived.

Preliminary observations on chloramphenicol in pantothenic acid deficiency give similar results. In thiamine-free diets, signs of deficiency could be prevented or delayed by 5 per cent ascorbic acid in the diet.—S. O. WAIFE

Pyridoxal Phosphate as Coenzyme of Histaminase. H. M. Sinclair. *Biochem. J.* 51: 10, 1952 (*Proc. Biochem. Soc.*)

The author briefly summarizes the evidence showing that pyridoxal phosphate (a form of vitamin B_6) is a coenzyme of histaminase. Among the bits of evidence is the fact that pyridoxine deficiency in rats results in a diminished histaminase activity in skin, intestine, and lung; and the skin of pyridoxine-deficient animals reacts more strongly to intradermal histamine than that of the controls. Furthermore, oral administration of an antihistamine greatly improves the lesions of the skin and mucocutaneous junctions in pyridoxine deficiency.

The author suggests that the most probable explanation of the skin and mucocutaneous lesions in pyridoxine deficiency is that the lesions are secondary to a vascular change produced by abnormal concentrations of histamine.—S. O. WAIFE

Vitamin B_6 and Hematopoiesis in the Rat. W. W. Hawkins, B. Lechow, and M. K. Evans. *Am. J. Physiol.* 170: 155, 1952.

The rat does not develop anemias as a result of deficiencies in Vitamin B_6. However, when a deprivation of this vitamin is produced, there is evidence that the hematopoietic system is nevertheless affected. Vitamin B_6 deficiency in the rat increases erythrocyte counts. In these experiments where vitamin B_6 was withheld the hemoglobin and hematocrit returned toward normal values more slowly than in controls. Cobalt did not produce a polycythemia.—M. J. OPPENHEIMER

White Blood Cells and Lymphoid Tissue in Vitamin B_6 Insufficiency. W. W. Hawkins and Mary K. Evans. *Am. J. Physiol.* 170: 160, 1952.

Desoxypyridoxine intensifies lymphopenia induced by vitamin B_6 deficiency in rats. However, desoxypyridoxine still produces lymphopenia when given with the vitamin. The thymus shows atrophy of lymph tissue and infiltration with fat. Anemic dogs (B_6 deficiency) showed a decrease in lymphocytes and neutrophiles. Pyridoxine corrected the anemia but not the leukopenia. Desoxypyridoxine plus vitamin B_6 restriction produced a mild anemia and a marked lymphopenia. These changes were reversed when desoxypyridoxine was discontinued and vitamin B_6 was added to the diet. The authors suggest that desoxypyridoxine produces a rapid vitamin B_6 deficiency.—M. J. OPPENHEIMER

Effect of Desoxypyridoxine on Acute Lymphatic Leukemia of Adults. D. R. Wein. *Proc. Am. Soc. Clin. Investigation.* Atlantic City, May 5, 1952.

Desoxypyridoxine is a potent antagonist of pyridoxine in animals and man, and its administration, even on a normal diet, results in certain characteristic hematologic changes, including granulocytosis, lymphopenia, and myeloid metaplasia of the spleen. These changes can be prevented or reversed by pyridoxine administration.

Five adult patients with acute lymphatic leukemia on a normal diet received up to 1.4 Gm. orally a day in divided doses for 80 days. No toxic effects were noted. In the three patients who were followed for some time, two had a marked fall in leukocyte count (from 90,000 to 8000, and 120,000 to 7600 per cmm.) and a regression of lymph nodes and general clinical improvement.

The effectiveness of pyridoxine deficiency in human leukemia will be studied with great interest.—S. O. WAIFE

Vitamin B_{12} in the Treatment of Viral Hepatitis. R. E. Campbell and F. W. Pruitt. *Am. J. M. Sc.* 224: 252, 1952.

Based on a study of 300 cases of viral hepatitis treated at the U. S. Army Hepatitis Center in Japan,

it was found that supplements of vitamin B_{12} (cyanocobalamin) were of significant value. In doses of 30 μg., vitamin B_{12} by mouth administered daily for the first five days of hospitalization led to a more rapid return of appetite and reduction in size of the liver. The total serum bilirubin values returned to normal more rapidly, and the total duration of the clinical disease was shorter in the treated group, compared to similar subjects treated by conventional methods. Relapses were fewer in the vitamin B_{12} treated group, although these patients were, if anything, more seriously ill than the groups receiving an adequate diet and bed rest.—S. O. WAIFE

Microbiological Studies on Materials Which Potentiate Oral Vitamin B_{12} Therapy in Addisonian Anemia. P. R. Burkholder. *Arch. Biochem.* 39: 322, 1952.

This paper discusses methods for the preparation of concentrates which possess intrinsic factor activity, and the assay of their potency in preventing vitamin B_{12} absorption by the bacteria which occur abundantly in the upper gastrointestinal tract of anemic patients. Strains of bacteria were isolated from the stomach and jejunal juice of Addisonian anemia patients, most of which had a strong tendency to absorb vitamin B_{12} from solution. Concentrations of hog stomach mucosa when added to incubating mixtures prevented the consumption of B_{12} by the bacteria. The author claims support for the theory that typical Addisonian anemia is a disease caused by the removal of vitamin B_{12} from the patient's digestive tract by a greatly increased microbial flora under conditions of achlorhydria and lack of intrinsic factor in the gastric region. Preparations of swine mucosa showing high potency in rendering vitamin B_{12} unavailable to bacteria are also rich in intrinsic factor as determined by feeding these preparations with B_{12} orally to patients, with resulting characteristic hematopoietic responses.—M. K. HORWITT

The Effects of Thyroid and of Choline and Inositol on Cholesterol Distribution in Rats Fed a High Cholesterol Diet. S. B. Weiss, L. Marx, and W. Marx. *Endocrinology* 50: 192, 1952.

Thyroid, administered to rats receiving 1 per cent cholesterol and 0.5 per cent bile salt in their diet, did not prevent significant hepatic sterol deposition, though plasma cholesterol was reduced to practically normal levels. The present experiments were designed to rule out the possible role of enhanced requirement for lipotropic substances in hyperthyroid rats. It was found that thyroid alone reduced the elevated plasma cholesterol and liver cholesterol and lipid accumulation produced by 2 per cent cholesterol added to the diet. Choline and inosotol, however, induced a marked elevation in plasma cholesterol, but reduced liver cholesterol and lipid. When thyroid plus choline-inosotol were administered to rats on the 2 per cent cholesterol diet at the highest dose level, the marked rise in plasma cholesterol, previously produced by choline-inosotol alone, was definitely modified by thyroid, and the reduction of liver cholesterol and lipid was further enhanced. It appears that the ability of thyroid to mobilize liver lipids and cholesterol is considerably augmented by lipotropic agents and that thyroid can partially overcome their hypercholesterolemic effects.—N. G. SCHNEEBERG

Cholesterol Metabolism in Pantothenic Acid Deficiency. R. R. Guehring, L. S. Hurley, and A. F. Morgan. *J. Biol. Chem.* 197: 485, 1952.

Pantothenic acid as a constituent of coenzyme A is involved in acetylation. Since acetate is used in the synthesis of cholesterol, the authors studied the effects of pantothenic acid deficiency on the ability of rats to metabolize cholesterol. Whereas feeding a complete diet containing 1 per cent cholesterol resulted in fatty livers and high levels of cholesterol in the liver and serum, the same cholesterol-rich diet did not produce a rise in liver lipids in pantothenic acid-deficient rats and only small increases in liver cholesterol and serum cholesterol.—M. K. HORWITT

Agammaglobulinemia. O. C. Bruton. *Pediatrics* 9: 722, 1952.

The author reports observations on a patient suffering from recurrent infections. In an effort to treat his infections immunization with various agents was undertaken and it was found that he did not respond with characteristic antibody titers in the serum. It was suspected that this failure to produce antibodies might be reflected in some derangement in the gamma globulin fraction. Electrophoretic analyses of his blood serum repeatedly gave negative results for gamma globulin, although the total serum protein and the A-G ratio were entirely normal. Subcutaneous administration of immune human serum globulin was followed by a subsidence of the infection without recurrence during the subsequent 14 months. Because the patient had been free of infections during his first $4^1/_2$ years of life it was presumed that this was an acquired disorder affecting the elaboration of gamma globulin. This is of importance in guiding others' observations of individuals susceptible to chronic and current infections and as a stimulus to studies directed at determining the factors controlling the level of gamma globulin in the serum.—C. D. MAY

Idiopathic Hypoproteinemia: Report of a Case of Transient Edema, Depression of Plasma Albumin and Gamma Globulin and Eosinophilia. J. B. Wyngaarden, J. D. Crawford, H. R. Chamberlin, and W. F. Lever. *Pediatrics* 9: 729, 1952.

The findings in a $3^1/_2$-year-old boy are reported in which transient depression of plasma albumin and

gamma globulin were encountered. The cause of this disturbance was not discovered and the relation to other instances of hypoproteinemia is discussed. The observation is of importance in directing attention to the possibility of transient disturbances in the fabrication of serum proteins which may lead to discovery of nutritional factors of importance in the maintenance of normal serum proteins.—C. D. MAY

Studies in Biochemical Adaptation. The Effect of Variation in Dietary Protein upon the Hepatic Arginase of the Rat. J. Mandelstam and J. Yudkin. *Biochem. J.* 51: 681, 1952.

Amounts of hepatic arginase in the livers of rats increased with increases of dietary protein and reverted to normal with reversion to a normal diet. This increase or decrease was complete within 2 or 3 weeks of changing the diet. Since the amounts of enzyme produced are directly proportional to the amounts of protein ingested, it was suggested that the mass action theory of enzyme production applies, since with the metabolism of more protein, there is a greater use of the enzyme in producing urea, and more ammonia is passing through the arginine cycle.—M. K. HORWITT

Effect of the Time Factor and Calorie Level on Nitrogen Utilization of Young Women. R. M. Leverton, M. R. Gram, and M. C. Chloupka. *J. Nutrition* 44: 537, 1951.

Sixteen young women served as subjects for the study for 54 days. The subjects ranged in age from 17 to 26 years, in height from 60 to 69 in., and in weight from 103 to 147 lb. They lived together in a small dormitory where the research staff supervised the entire program. These subjects were divided into two groups. One had a daily intake of about 43 Gm. of protein and the other of about 63 Gm. The study was concerned with the effect of the time factor and calorie level on nitrogen utilization.

The effect on nitrogen excretion of the absence or presence of animal protein furnished by 240 Gm. milk in the noon meal, and the effect of a calorie level of 1800 as compared with one of 2400 were determined. The group on the lower protein intake had a significantly lower urinary nitrogen excretion when the animal protein was furnished as milk in the noon meal than when it was absent. The group on the higher protein intake showed no difference in nitrogen excretion related to the presence or absence of protein in the noon meal.

There was a marked reduction in nitrogen excretion by both groups when the calories were increased from 1800 to 2400 and yet animal protein was absent from the noon meal. The nitrogen sparing action of the additional calories was greatest at the lower protein intake. The authors conclude that the lower the intake of protein and calories, the greater is the need for including high-quality protein in each meal, if nitrogen is to be well utilized.—B. SURE

Nitrogen Retained by Six Adolescent Girls from Two Levels of Intake. F. A. Johnston and D. Schlaphoff. *J. Nutrition* 45: 463, 1951.

The subjects were 6 girls between 13 and 14 years of age whose heights ranged from 151.6 to 169.1 cm. and whose weights ranged from 35.8 to 56.4 Kg. at the beginning of the study. While all were in good health as judged by physical examination, two were underweight by more than 10 per cent, and one was overweight by more than 10 per cent above the average weight. This study was undertaken, since the amount of nitrogen which girls of this age need to retain for good health and normal growth is not known. They need to retain enough for growth and development and also enough to cover the nitrogen lost from the body which is not measured in the usual balance experiment.

During the first experimental period of three weeks, the mean daily intake of nitrogen was 12.2 Gm., corresponding to 76.2 Gm. of protein. The mean daily amount of nitrogen retained from the diet by the 6 subjects was 1.42 Gm. or 29.9 mg. per Kg. During the second experimental period of 4 weeks, the mean daily intake of nitrogen was 13.97 Gm., corresponding to 87.3 Gm. of protein. On this diet the daily amount of nitrogen retained was 2.17 Gm. or 43.7 mg. per Kg. The mean intake of 76.2 Gm. of protein per day was probably adequate for these subjects. The intake of 87.3 Gm. protein was undoubtedly more than adequate.—B. SURE

Nitrogen Loss in the Feces: The Variability of Excretion in Normal Subjects on Constant Dietary Intakes. V. Toscani and G. D. Wheadon. *J. Nutrition* 45: 119, 1951.

A survey was made of the variation in fecal nitrogen excretion of 4 normal subjects on constant dietary intakes for 4 to 5 months. There were 7 studies which ranged in length from 14 to 19 metabolic periods of 7 days each. In 6 of these studies the subjects received a constant dietary intake of 90 Gm. protein, 14.42 Gm. nitrogen. The caloric content of the diets, as well as the content of calcium, phosphorus, and potassium, were also kept constant throughout.

The stools were marked by giving the subjects orally 0.2 Gm. of carmine at 9 p.m. on the last day of the period. Stool specimens were collected directly into enamel containers, which were then covered and placed in a refrigerator at 5°C. Drying of the refrigerated stools was begun within 48 hours. The dried feces for the period were pooled, weighed, thoroughly ground and mixed, and stored in capped glass bottles for subsequent analysis.

During 99 metabolic periods of 7 days each, in which the nitrogen intake was identical among the 4 subjects (14.42 Gm. daily), the fecal nitrogen ranged from 0.91 to 2.22 Gm. and the mean percentage fecal N/intake N ranged from 7.9 to 13.0 per cent. Variation in fecal nitrogen excretion was more marked from

one subject to another from period to period in the same individual.

Since appreciable variation in fecal nitrogen loss occurred under optimum conditions for constancy, the authors conclude that it would be unwise in an individual experiment to assume fecal nitrogen to be either 10 per cent of the intake nitrogen or a fixed value of 1.3 Gm. For accuracy, direct analysis of fecal nitrogen should be made.—B. SURE

On the Nature of the Interdependence of the Adrenal Cortex, Non-specific Stress and Nutrition in the Regulation of Nitrogen Metabolism. F. L. Engel. *Endocrinology* 50: 462, 1952.

This paper represents a continuation of a series of investigations concerning the role of the adrenal cortex in nitrogen metabolism, the site of action of adrenal hormones upon nitrogen metabolism, and various factors modifying this action. Previous studies demonstrated that the catabolic or anti-anabolic action of adrenal steroids could be reduced by the intravenous administration of glucose or amino acid, but not by albumin, plasma protein, or a fat emulsion.

The present experiments demonstrated that stress (formalin, insulin, epinephrine) immediately increased urea formation in the nephrectomized rat, but not in the adrenalectomized-nephrectomized rat maintained with saline and DOCA, whereas the injection of adrenal cortical extract or ACTH produced only a delayed increase in urea formation in the nephrectomized rat. Pre-treatment with adrenal cortical extract resulted in an immediate increase in urea formation following mild stress, whereas mild stress alone produced no change. At least three interdependent variables modified nitrogen metabolism during stress—the stress itself, the adrenal cortex, and the nutritive state of the organism.

The evidence from this work and other experiments by the same author, coupled with observations by Ingle and his group, have led to the concept of the "permissive" role of the adrenal cortex during stress, wherein the organism requires a certain circulating level of adrenal steroids in order to respond to stress, though the adrenal hormones themselves are not directly responsible for the metabolic and other changes following a stressful stimulus This view contradicts the original concept that stress-induced changes in the organism are a direct result of a discharge of adrenal hormones in response to stimulation of the hypothalamic-pituitary-adrenal system.—N. G. SCHNEEBERG

Mechanism of Epinephrine Hyperglycemia. M. Somogyi. *Endocrinology* 40: 774, 1951.

The author takes issue with the generally accepted hypothesis that epinephrine-induced hyperglycemia can be attributed solely to hepatic glycogenolysis. So thoroughly accepted has been this explanation that the blood sugar response to an injection of epinephrine has been advocated as an index of hepatic glycogen stores (*Am. J. Med. Sci.* 217: 554, 1949). By demonstrating a significant reduction in the A-V blood sugar difference after the injection of epinephrine combined with the oral feeding of glucose as compared to the substantial A-V difference following the ingestion of glucose alone the conclusion is reached that depression of the rate of peripheral glucose assimilation by epinephrine action plays an important part in the production of epinephrine hyperglycemia.

This important contribution will be strengthened by further experimental studies which will possibly include (a) proof that the observed changes were not due to an accelerated rate of blood flow, a factor commented upon by the author, (b) a demonstration that epinephrine does not interfere with intestinal assimilation of glucose since this involved a phosphorylative mechanism similar to that involved in its peripheral accumulation, (c) that the results can be reproduced in subjects whose livers have been depleted of glycogen, (d) a demonstration of the inhibition of glucose assimilation by epinephrine utilizing in vitro experimental techniques, (e) a demonstration of epinephrine-induced retardation of the rate of blood sugar fall in the hepatectomized (eviscerated) animal.

Finally, the author's theory does not explain the salutary effect of epinephrine in acute hypoglycemia, a phenomenon that must presuppose the rapid cellular assimilation of glucose.—N. G. SCHNEEBERG

Nature of the Stimulating Action of Insulin on Lipogenesis from Acetate in Fasted Rat Liver. M. S. Masri, I. Lyon, and I. L. Chaikoff. *J. Biol. Chem.* 197: 621, 1952.

The fasted rat has a diminished ability to convert acetate to fatty acids. This failure in hepatic lipogenesis has been related to depressed glycolytic activity and to the reduction in circulating insulin. Using *in vitro* techniques on rat liver slices, it was noted that insulin alone failed to augment lipogenesis or CO_2 formation from acetate in the liver of the fasted rat, whereas glucose alone stimulated both. When insulin and glucose are added together, lipogenesis was stimulated to a greater extent than that observed with glucose alone.—M. K. HORWITT

Further Studies on Influence of Age and Diet Upon Reproductive Senescence in Strain A Female Mice. M. B. Visscher, J. T. King, and Y. C. P. Lee. *Am. J. Physiol.* 170: 72, 1952.

The authors have shown that the rate of aging in physiological characteristics can be changed by diet in mice. The criteria used were the ability to form placentae, number of living compared to dead at full term, and the ability to nurse the young to weaning. On the diet used, no live litters are delivered after 10 months. This same diet is adequate for reproduc-

tion in young mothers. When calories of lard and dextrose are reduced one-half and the other factors held constant for 13.2–15.5 months, the failure of reproduction is much delayed. When calories are restored, these mice deliver young better than those continuously full-fed for 6 months. The authors have properly stressed the fact that intensive studies of these phenomena in mice will lend a wealth of valuable information relating to senescence.—M. J. OPPENHEIMER

Low Sodium Diet and Resin Therapy in Hypertension. R. S. Griffith, O. M. Helmer, and K. G. Kohlstaedt. *Fed. Proc.* 11: 59, 1952.

Fifteen patients with essential hypertension received a 200-mg. sodium diet. In addition, a mixture of cation-anion exchange resins was administered. It was necessary to administer supplementary potassium at the time the body was maximally conserving sodium. Eight patients had a drop in blood pressure to normal levels within two weeks to a month. The blood pressure of two other patients decreased significantly. Five patients did not respond. Following stabilization of blood pressure, the subjects received a 1.5 Gm. sodium diet and the resin dosage was increased so as to maintain urine sodium at the same level. No rise in blood pressure occurred under this regimen. With the reduction in hypertension, the body weight and transverse cardiac beat in diameter were decreased.

In those subjects whose blood pressure was reduced to normal there was evidence of adrenal stimulation, as shown by a drop in absolute eosinophiles and an elevation in plasma renin-substrate concentration. These findings were not found in patients who showed no lowering of blood pressure.—S. O. WAIFE

Self-Demand Feeding in a Maternity Unit. R. S. Illingsworth and D. G. H. Stone. *Lancet* 1: 683, 1952.

Comparable groups of babies were fed respectively on a rigid schedule of 6 feedings in 24 hours and a "demand" feeding schedule. It was shown that the "demand" group gained weight faster than those on a rigid schedule because of more frequent feedings. By the ninth day, almost 50 per cent of the demand group had regained their birth while only 36 per cent of the rigid group had done so. There was less overdistension of the breast and nipple soreness in the demand group, and a larger percentage of the babies of this group were fully breast-fed, indicating that there was a more favorable effect upon lactation.—C. R. SHUMAN

Intravenous Iron Therapy in Iron-Deficiency Anemia of Infancy and Childhood. B. Dickstein, I. J. Wolman, C. Tan, B. Slaughter, H. Butson, and R. Cohen. *Am. J. Dis. Child.* 84: 52, 1952.

The authors report their experience with the treatment of 80 infants and children with intravenous injections of saccharated iron oxide. There were no severe reactions encountered in 21 injections. The hemoglobin values were restored rapidly and completely in nearly every instance. The authors proposed that intravenous administration of iron is practicable and effective and may be indicated when oral administration of iron cannot be depended upon because of its not being tolerated or dependable administration of oral therapy cannot be anticipated. —C. D. MAY

Coeliac Disease: Gastrointestinal Studies and the Effect of Dietary Wheat Flour. C. M. Anderson, A. C. Frazer, J. M. French, J. W. Gerrard, H. G. Sammons, and J. M. Smellie. *Lancet* 1: 836, 1952.

A group of 10 children with coeliac disease was found to have essentially the same biochemical and radiographic findings as those described in adult patients with idiopathic steatorrhea. These alterations consisted of normal pancreatic enzyme concentrations, increased fecal fat, decreased chylomicron counts, a flat glucose tolerance curve, and flocculation of the barium meal in small intestine x-rays.

Striking clinical improvement was noted in all cases when a wheat-free diet was employed. This was accompanied by an increase in the absorption of fat. The abnormal radiographic appearance of the bowel became normal. Upon the re-introduction of wheat flour (but not wheat starch) into the diet, the symptoms of coeliac disease reappeared. It would appear that the clinical disturbance is related to the gluten fraction of wheat flour.—C. R. SHUMAN

The Effect of Cortisone on Nontropical Sprue (Idiopathic Steatorrhea). A. B. Taylor, E. E. Wollaeger, and M. W. Comfort. *Gastroenterology* 20: 203, 1952.

The effect of cortisone on 6 patients with non-tropical sprue was studied. Observations were made on clinical response, change in bowel function, and general metabolic effects, in addition to miscellaneous laboratory studies. To avoid misinterpreting natural changes for effects of cortisone, periods of cortisone administration were preceded by, alternated with, and followed by control periods or periods in which a similar appearing placebo was administered. Cortisone was given in one case by the intramuscular route; in the remaining cases it was given by mouth. The daily dose of cortisone was usually between 25 to 100 mg., although varying dosages were given. The intramuscular preparation was administered once a day, while the medication for oral use was divided into 2 to 4 doses and given over the 24-hour period.

Cortisone appeared to be equally effective by both the intramuscular and oral routes. There was a lag between the initiation of treatment and the development of detectable response. Subjective improvement occurred before laboratory evidence of improvement

could be determined. In every case definite subjective and objective improvement was observed. Appetite and strength improved; stools decreased in number and became more nearly normal in consistency; symptoms of abdominal cramping and distention virtually or completely disappeared. The amount of solids, water, fat, and nitrogen in the feces decreased and prothrombin time returned to normal. No evidence was obtained that absorption of carbohydrate from the bowel of the sprue patient, as measured by oral glucose tolerance tests, was influenced by cortisone. The supplemental administration of calcium as an adjuvant to cortisone seemed wise. Hypertension developed in 1 patient and edema occurred frequently when the hormone was given in 100-mg. doses. Cortisone-induced remission persisted for periods of 1 to 6 weeks after withdrawal of the drug.

The authors conclude that cortisone offers the most effective means of treating non-tropical sprue in exacerbation, but believe that its importance in the long-term management of the disease remains to be evaluated.—J. E. BERK

Gastrointestinal Transit. R. D. Goodman, A. E. Lewis, E. A. Schuck, and M. A. Greenfield. *Am. J. Physiol.* 169: 236, 1952.

The authors define gastrointestinal transit as the fraction of the quantity of material contained in a given segment which is delivered to its adjacent distal segment per unit of time. This is a new concept of transit which gives different data from biochemical or balloon methods. This is importantly related to the availability of food stuff for absorption. Equations and techniques are presented. An aqueous solution of Evans Blue (30 mg./cc.) is introduced into the stomach and the animals (rats) allowed food and water *ad lib.* Animals are sacrificed at 1-, 2-, 3-, and 6-hour intervals. Clamps are quickly placed on the lower end of the esophagus, pylorus, and terminal ileum. The gastrointestinal segments are analyzed for Evans Blue. There is a close correlation between the mathematically derived and experimentally determined values for the first three hours.—M. J. OPPENHEIMER

Effects of X-Irradiation on Gastrointestinal Transit and Absorption Availability. R. D. Goodman, A. E. Lewis, and E. A. Schuck. *Am. J. Physiol.* 169: 242, 1952.

A decrease in gastric emptying is noted within 24 hours after irradiation. Transit time from pylorus to ileocecal valve is insignificantly changed. Absorption availability is, however, markedly reduced. This change is maximum 4–7 days after irradiation, and is still abnormal on the 21st day. The authors suggest that the increased absorption availability depends largely upon changes in gastric transit.—M. J. OPPENHEIMER.

Dietary Factors Influencing Output of Bile Acids: Endogenous Production of Bile Acids. D. F. Magee, K. S. Kim, V. C. Pessoa, and A. C. Ivy. *Am. J. Physiol.* 169: 309, 1952.

The average output of endogenous cholate in external bile fistula dogs is approximately 100 mg. per Kg. when bromsulphthalein clearance is normal. It is pointed out that this value is double that obtained by previous workers. Different methods or undetermined liver damage may explain the discrepancy. When the amount of cholate secreted is low this was found to be significantly correlated with bromsulphthalein retention. The authors consider that a decrease in production of cholate may be due to extrahepatic bile obstruction or an ascending hepatitis in the dog with attendant hepatic disturbance. Methods for computing the cholepoietic potency of a diet are presented.—M. J. OPPENHEIMER

The Small Intestine as a Factor in Regulation of Eating. R. G. Hill, E. C. Ison, W. W. Jones, and J. W. Archdeacon. *Am. J. Physiol.* 170: 201, 1952.

Food intake was limited when hypertonic glucose was introduced into the small intestines of dogs via a fistula. Limited reductions in intake were encountered when fulness, distension, or small intestinal motility were produced by non-nutritive fiber. Tyrosine was ineffective. These experiments indicate that the reduction of food intake depends more on generalized metabolic effects after absorption from the small intestine or upon the local effects of hypertonicity. The mouth and stomach are ruled out in these experiments.—M. J. OPPENHEIMER

A Study of Carbohydrate and Fat Absorption from the Normal and Diseased Intestine in Man. I. The Absorption and Excretion of D-Xylose. F. S. Brien, D. A. Turner, E. M. Watson, and J. H. Geddes. *Gastroenterology* 20: 287, 1952.

Samples of blood and urine obtained from normal subjects were analyzed for free pentose content before and at hourly intervals for 5 hours after the ingestion of 25 Gm. of d-xylose in 500 cc. of water. The blood xylose concentration reached a maximum level within one hour after the ingestion of d-xylose and approached fasting values within 5 hours. Blood xylose curves obtained in 12 normal subjects displayed a constancy of the curves from individual to individual. This constancy of the xylose tolerance test was of a different order from that of the glucose and fructose tolerance tests. Some xylose was rapidly excreted by the kidneys, and urine xylose concentrations approached fasting values within 5 hours. Approximately 19 Gm. of d-xylose could not be accounted for in the urine, indicating that some of the sugar is destroyed in the tissues. A change in the plasma inorganic phosphate concentration followed the ingestion of d-xylose in every subject tested; a drop followed by a consistent rise above fasting levels

occurred in 11 subjects, while a consistent rise from fasting levels was seen in 3 instances.

The authors conclude from these observations that the d-xylose is phosphorylated during absorption and that the xylose tolerance test is the most reproducible test of intestinal absorption. They suggest further that the urinary excretion of d-xylose may have application as a test of kidney function. In the presence of decreased glomerular filtration, the amount of xylose excreted by the kidneys may be diminished while the blood xylose concentration is increased above normal as a result of "backing up" of the sugar. Impaired absorption from the intestine alone would result both in diminished blood xylose concentration and a reduced amount of xylose excreted in the urine.—J. E. BERK

A Study of Carbohydrate and Fat Absorption from the Normal and Diseased Intestine in Man. II. Changes in the Serum Lipids in Man after the Ingestion of Butterfat with and without Tween 80 (Sorlate). F. S. Brien, D. A. Turner, E. M. Watson, and J. H. Geddes. *Gastroenterology* 20: 294, 1952.

Groups of normal subjects were studied to determine the effect of Tween 80 on the serum concentrations of total and free cholesterol, total fatty acids, and total phospholipids following the ingestion of a fatty meal. After the ingestion of 50 Gm. of butterfat together with 1.5 Gm. of Tween 80, peaks in the concentration of total fatty acids and total phospholipids in the serum were reached earlier than when the detergent was not given with the fatty meal. The serum concentrations of total and free cholesterol were not significantly altered following the ingestion of the fat meal, with or without Tween 80.—J. E. BERK

Fat Absorption and Chylomicronemia. L. Marder, G. H. Becker, B. Maizel, and H. Necheles. *Gastroenterology* 20: 43, 1952.

Chylomicron studies and nephelometric measurements of the Tyndall effect of serum were conducted on the sera of 12 young subjects (20 to 30 years of age) and 12 old people (68 to 83 years of age), before and at intervals after ingestion of special fat meals. The study was prompted by previous observations indicating that a number of digestive mechanisms change with advancing years. It was thought that the chylomicron technique might also demonstrate a difference in fat digestion and absorption in young and old age groups. The results demonstrated a difference in the chylomicron response to fat meals in young and old people, the older age group showing an increased concentration of larger particles in the serum. Only a slight difference in nephelometric values was apparent in the two groups. These observations were interpreted as suggesting that fat absorption in the blood of young and old people is similar, but that the particle size in transport is different. It is suggested that the degree of chylomicronemia and the size of the particles depends on the state of hydrolysis of the fat, and since this is influenced by lipose, deficiency in pancreatic lipose may be sufficient in the aged to cause more unsplit fat to be made available for absorption. Smoking appeared to cause an increased and prolonged chylomicronemia, at least in the young group. The mechanisms responsible for this are not clear. There is a possibility that some relationship exists between chylomicronemia and the production of degenerative vascular disease, but this remains to be proved.—J. E. BERK

Effect of Prolonged Intragastric Feeding on Oral Food Intake in Dogs. I. Share, E. Martyniuk, and M. I. Grossman. *Am. J. Physiol.* 169: 229, 1952.

Dogs with gastric fistulae were fed intragastrically four hours after their feeding by mouth. This was continued daily for several weeks. If the intragastric feeding was in excess of one-third of the calories orally ingested during the control period, the oral intake was decreased. However, the sum of oral and gastric calories was always greater than that of the control period. When material without caloric value was introduced into the stomach there was no effect unless such inert substances were introduced in large amounts just before meals. The caloric intake by mouth was reduced when water-filled balloons were allowed to remain in the stomach for several weeks.

Duration of sham feeding (in dogs with esophageal fistulae) was decreased inversely with the amount of food introduced intragastrically, or if food or a water-filled balloon were introduced just before feeding.

Two factors are operating in these experiments to control food intake. Gastric distension is certainly demonstrated to be important. Moreover, there is a systemic factor, independent of the period of absorption and distension, which operates for at least twenty hours after the last intragastric feeding to depress oral intake.—M. J. OPPENHEIMER

Stress of Realimentation with Protein or Carbohydrate following Prolonged Fasting. C. M. Wilhelmj, T. F. McGuire, and E. B. Waldman. *Am. J. Physiol.* 169: 248, 1952

After prolonged fasting, ingestion of large amounts of carbohydrate constitutes a more severe stress upon the cardiovascular and gastrointestinal systems than equal amounts of protein. Realimentation with small calorie meals causes little disturbance. Gradual increase in intake can be satisfactorily controlled by observations of pulse rate and blood pressure.—M. J. OPPENHEIMER

The Chemical Manipulation of Food. E. Mellanby. *Brit. Med. J.* 2: 863, 1951.

In this lecture, it is properly emphasized that medical scientists must assume a greater responsibility in the chemical processing and manipulation of foods.

In the U.S.A. the Food and Drug Administration has maintained a careful surveillance in these matters and has extensive laboratory facilities and staffs in order to protect the public from adulterations or other misuse of foods. Possibly some of the illnesses of our modern civilization are the result of foods treated with chemicals or the consequence of the degradation of the nutritional qualities of food through the removal of important constituents.

Among the chemical substances utilized in the processing of foods are sweetening agents, certain of which are highly toxic for animals, and coloring matter, among which are the carcinogenic azo dyes. The high consumption of bread demands attention as to the chemical agents incorporated into it for the purpose of preventing staleness and improving its appearance. The substances used for these purposes lower the nutritional quality of the product and may prove to be of a toxic nature for the human just as they are for animals. It is pointed out that the miller reduces the energy value of bread by 15 to 20 per cent and the baker by 9 to 20 per cent through the use of various methods of treatment of the flour.

This paper is of considerable importance in that the author has carefully outlined the major aspects of the problem of food treatment and its effect upon the nutritive value of foods.—C. R. SHUMAN

Purification of a Toxic Substance from Defatted Soy Bean Flour. I. E. Liener and M. J. Pallansch. *J. Biol. Chem.* 197: 29, 1952.

Soy beans, in common with certain other leguminous seeds, contain a toxic substance which will inhibit growth and agglutinate red blood cells. The problem as to whether the growth-inhibiting properties which have been associated with anti-tryptic activity and hemagglutinating activity are closely associated with the same protein component was partially resolved by the preparation of a toxic component from defatted soy bean meal which had marked hemagglutinating action, but was essentially devoid of anti-tryptic activity.—M. K. HORWITT

Nutrition Resurvey in Bataan, Philippines, 1950. H. B. Burch, J. Salcedo, Jr., E. O. Carrasco, and C. L. Intengan. *J. Nutrition* 46: 239, 1952.

Biochemical measurements of the effects of the enriched rice program in Bataan are reported in this paper. The measurements were made in December 1950 after the population had received rice, enriched with iron, thiamine, and niacin for two years. The marked increased in blood and urinary thiamine and in hemoglobin indicate a major change in the intake of thiamine and iron in the diet. These increases are mainly attributable to the consumption of enriched rice, since its introduction constituted the only major dietary change. The finding of undesirably low urinary riboflavin points to the needs of further enrichment of rice with this vitamin. The dietary surdiet of the population of Bataan, which is due to a low intake of vegetables, and a critical lack of calcium.

The chemical findings on changes in thiamine levels and in hemoglobin concur with the clinical reports on improvement in health of the people following the inauguration of the enriched rice program.—B. SURE

Principles of Emergency Feeding for a Large Metropolitan Area in Catastrophe. R. S. Goodhart and N. Jolliffe. *Amer. J. Public Health* 42: 373, 1952.

The authors are concerned with a design for careful, controlled emergency feeding in areas the size of New York City in the event of hostilities. It is considered wise to divide individuals into groups: (a) evacuees, i.e., healthy individuals not engaged in essential emergency duties whose caloric intake is limited to 1600 daily; (b) essential workers who are to be provided with a 1400 calorie meal every four hours while working and (c) special groups including infants, children up to 4 years of age, pregnant and lactating women, all of whom need special consideration; (d) severely injured and burned patients for whom 3500 calories daily is allotted.

Considerable reliance is to be placed upon an enriched white bread made with 4% non-fat milk solids which will supply 1250 calories per lb.; 38 Gm. of protein, and 1.1 mg. thiamine.

It is considered neither necessary nor desirable to maintain special stocks of processed emergency rations (such as U. S. Army K rations) but rather to rely on each family to keep a "reserve shelf" of things other than bread. A detailed suggestion for such a reserve shelf is given. This dolorous article should be consulted in its original form by those interested in its details. It reflects considerable thought and is very inclusive. The authors grimly remind the reader that "the explosion of two Bikini-type atomic bombs over New York City would directly affect 3,000,000 persons and would require the services of at least 500,000 emergency workers".—A. J. STEIGMAN

Dental Caries in Rats Fed a Diet Containing Processed Cereal Foods and a Low Content of Refined Sugar. F. J. McClure. *Science* 116: 229, 1952.

A diet has been developed which does not involve a coarse particle factor and in which the content of sugar is relatively low (18 per cent). This diet is obviously inadequate in lysine and suggests a somewhat new approach to problems of nutrition in relation to dental caries. The caries involvement of the lingual, buccal, and proximal molar tooth surfaces of the rats is strikingly similar to human dental caries.—M. K. HORWITT

Psychogenic Elements in Anorexia. J. de Moragas. *Acta pediatr. espań.* 10: 198, 1952.

This is an essay on the nature of hunger and appetite and the role played by physiological and imaginative factors in both.

Anorexia in children is interpreted in terms of "the anguish created in all of us by the struggle between the desire to remain what we are and our desire to progress towards what we are not yet." In the child, the "instinct of self-preservation" may take the form of the desire to remain a child. Thus, the constant admonition to "eat and you'll grow up to be a man" may seem a threat rather than an inducement, and the child may resist what is offered him in order to maintain himself in a status where he dominates his mother. Infantile anorexia is especially common, according to the author, where the father is weak or absent, the mother dominant and anxious. In opposing the solicitations of the too authoritative mother, the child retaliates and makes her his victim.

The desire for permanence implicit in childish anorexia may be complicated by the will to regression, when jealousy situations arise. In an attempt to induce the child to eat, the zealous mother may present him with too wide a choice. The child, feeling quite correctly that the necessity of making decisions is a part of the adult world he is staving off, may take refuge in anorexia. In the older child, anorexia often appears simultaneously with the school years, as part of the same rejection of progress toward adulthood.

Of all the various factors leading to anorexia, the author considers the most important ones to be: (1) the child's desire for permanence; (2) the mother's anxiety; (3) compulsion; (4) over-feeding.

Against the child's desire for permanence, it is necessary to use educational methods which stimulate him toward the progress of his personality in an optimistic way. The mother must be reëducated, must be convinced that her anxiety is harming the child. She must be shown where the real good of her child lies, and that it does not consist exclusively in the conservation of health—the importance of which is all too often exaggerated in the mother's mind through the fault of the pediatricians themselves, "who sometimes attempt to reduce all their science and art to weight and calorie tables and a recipe for pap."

If necessary, the child must be temporarily removed from the circle of anxious female relatives who hover over him with perpetual comments on his color, his weight, and his spells of nausea. Away from this audience, in tranquil surroundings, "where food is given in a discreet and rational way and is not presented as the basic object of life, but as one of the means of remaining alive and realizing our authentic objectives," the child's resistance may be overcome.—C. J. Howell